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Synopsis of the Panel Discussion: The Question of Resistant Staphylococci and Tubercle Bacilli*

The Problem of Bacterial Resistance

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Bacterial resistance first became a problem with the chemotherapy of gonorrhea. In consequence of irregular or improper treatments, one noted more and more resistance to sulfonamides. Subsequently, these cases were treated with penicillin. Gradually, however, penicillin-resistant gonococci were found. Even so, with the combined use of sulfonamides and penicillin, the problem of gonorrhea has been solved in Europe.

In contrast, penicillin-resistant staphylococci have been noted. These show an increase of dangerous proportions in some hospitals. There are staphylococcus carriers. The risk of resistant-staphylococcus infection is noted not only in surgical and obstetrical clinics, but also in effective disinfection of the hands with preparations which are not quite reliable. This does not mean, of course, there are no potent and useful skin disinfectants. Aggressive advertising of preparations of inferior value is not likely to help in this situation.

It is of utmost importance to resort to the use of chemicals and antibiotics which, when administered in adequate dosage, produce a sustained, effective blood plasma level. The situation concerning the chemotherapy of tuberculosis is even worse than that of other infectious diseases. Unfortunately, some pharmaceutical firms are making products which do not prove to be effective when tried in animal experiments. Moreover, it may be desirable to control the efficacy of such new drugs by means of examining the bacteriostatic capacity of the blood serum during administration of these medicaments. This suggestion is justified by publications which report of the occurrence of INH-resistant tubercle bacilli in 30 per cent of the patients. In this connection, it is well to keep in mind the urgent need for ambulatory treatment of tuberculosis. To illustrate this point, I may mention that in India there are more than two and one-half million tuberculosis cases in need of treatment, while there are only 25,000 beds for this purpose.

In view of the occurrence of bacterial resistance to INH, it seems desirable that one should resort to combined treatment with INH and PAS. The administration of the latter, however, is difficult because to render PAS really effective, it should be given in large doses intravenously. This, of course, is not possible unless the patient is in an institution. For the same reason, combined treatment with INH and streptomycin is impracticable outside of institutions.

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It is my recommendation that the treatment of tuberculosis should be carried out with INH and sulfathiozole with doses between 5 to 7 mg. per Kg. According to our experience, still better results can be expected from Nicoteben (INH + thiosemicarbazone). I have not seen any other drug which is bound to give as effective blood levels against INH-resistant tubercle bacilli as these combinations. It is possible that INH gives a more potent and longer lasting effect as has been thought generally, even in instances where resistant tubercle bacilli may appear. Also, in case of failure, one can resort to other more effective INH derivatives, such as Heteroteben. It seems expedient to have some drug in reserve in case resistance to INH should develop. Foremost of these drugs is Nicoteben which can be administered orally and the composition of which is: 8 parts of Neoteben, plus 2 parts of isonicotinaldehydethiosemicarbazone.

It is gratifying to note that with the adequate use of specific therapy, the pulmonary tuberculosis mortality rate in some hospitals after the war has been reduced from 43 per cent (prior to the use of chemotherapy) to 4.3 per cent. As a matter of fact, with more expert use of available specific drugs, the mortality rate is bound to be lowered still farther.

To be sure, this substantial change in the tuberculosis situation is due chiefly to chemotherapy and not to decreased virulence of tubercle bacilli or an increase in the natural resistance or increase in the immunity of the body. Our ultimate purpose should be an early and effective treatment of every case of tuberculosis with INH and with its useful derivatives or combinations of INH and sulfathiozole or INH + thiosemicarbazone (for instance, Conteben, Tb I, Tibione and others).

Reports have been published in the medical literature in England and France on the occurrence of tuberculosis caused by primarily-resistant mycobacteria and atypical mycobacteria. This problem will have to be given careful investigation. In closing, I want to emphasize again the cardinal precept of tuberculosis therapy should be the slogan: prevent the development of open tuberculosis and cavity formation by early treatment.

The Possible Role of Mutation in Resistance and Atypical *M. Tuberculosis*

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It was pointed out that all variations in tubercle bacilli are explainable by the laws of biology. While there may be phenomena not yet clearly understood in the life of bacteria, the mutation theory of DeVries seems to be adequate to explain most of the changes that have appeared and are continuing to appear as they do in other forms of life.

Even before the recent work, the mutation theory was quite plausible; where changes could be demonstrated by stimulants, such as the x-ray and chemicals on certain species of life. The biochemical and x-ray identification of the structure of giant molecules in the chromosomes are more revealing and convincing.

The work of Tatum in the biochemical field and Watson and Crick in the use of x-ray diffraction in locating atoms in the molecules, have been outstanding.

Major displacements occur, however, so that a variation in the progeny may be demonstrated as an "atypical" form of acid-fast bacillus resembling *M. tuberculosis* or one having resistance to one or more of the antimicrobial drugs.

These variations are a continuing process in all living things and help to explain the formation of new species as well as the wide spread of species on the earth. Every species is said to form mutants at a constant rate for each species.

When there has been a radical change in the environment, a mutant may result and will grow when all the other forms, including the parent strains, are suppressed or are over-grown.

Use of antimicrobial drugs has brought the phenomenon into clearer perspective. The drugs have blocked the formation of new molecules leaving the mutants free to over grow the parents as resistant forms.

The question whether drugs cause mutation is still unanswered, but the wiping out of the sensitive parent forms no doubt leaves a greater number of atypicals to deal with. Since the era of antimicrobials, many more variants in the form of "atypicals" or resistant forms have been permitted to develop.

Significance of Primarily-Resistant Tubercle Bacilli

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I consider tubercle bacilli as resistant when they are at least four or five times less susceptible to antimicrobials than the internationally accepted stock of H37R. The former microorganisms show a growth when the concentration of INH is 0.1 to 0.2 gamma or higher, and the concentration of PAS is 1 gamma and when the concentration of streptomycin is 10 gamma or higher. For Conteben, the figure is 10 gamma or higher.

I have collected observations on the use of INH, streptomycin, PAS and Conteben in 1546 children and 1233 adults while exploring the effect of four chemotherapeutic agents. In addition, 2615 adults were tested for INH resistance. In children, we have found primarily-resistant tubercle bacilli in 6 per cent; of this, 1.8 per cent were infected with INH-resistant and 1.2 per cent with streptomycin and multi-drug resistant tubercle bacilli; PAS-resistant infection occurred in 1.6 per cent and Conteben-resistant infection in 0.2 per cent. In adults, we have found primary resistance of tubercle bacilli to all four chemotherapeutics in 2.8 per cent.

I have noted that in children, the incidence of primarily-resistant tubercle bacilli to INH increased from 1955 to 1956 and then the incidence remained stationary. Resistance to PAS is showing a declining curve. The same holds true of streptomycin, except that the latter showed a substantial increase in 1959. I have reason to believe this increase does not reflect a true higher incidence. Conteben resistance is minimal.

In adults, an increase in the primarily-resistant incidence was noted, which is attributable mostly to an increase in streptomycin resistance. Available reports from abroad, as well as from Germany, show the incidence of primarily-resistant tubercle bacilli varies according to geographic location. This means there is a need for further clarification of the epidemiologic status.

Relative to the clinical significance of these microorganisms, we have made the following observations: children with hilar lymph node involvement, with or without associated lung lesion, respond to chemotherapy as satisfactorily as cases with sensitive tubercle bacilli. Only 2 of 48 patients failed to respond to treatment. The degree of resistance made no difference in the clinical picture, but recovery was lower in INH- and multi-resistant cases.

The situation is much worse in childhood meningitis and in tuberculosis of adolescents and adults. Normal recovery was noted only in 38 per cent and 44 per cent, respectively.

In pulmonary tuberculosis of adults, the situation is still worse, particularly since unfavorable therapeutic results were noted in infections with tubercle bacilli primarily resistant to INH and streptomycin.

In view of the unfavorable course of disease in the aforementioned cases, one should go on record with the following conclusions: it is mandatory to prevent infection with these microorganisms. To achieve this, children in a tuberculous environment should be given BCG vaccination, as well as INH prophylaxis, when contact persons are not under satisfactory treatment and supervision. Under any circumstance, every effort should be exerted for the isolation, better supervision of open cases of tuberculosis, and for the early detection of possible breakdowns.

Clinical Significance of Bacterial Resistance to Tuberculostatics

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I have studied this problem in 300 tuberculous patients. In patients infected with sensitive tubercle bacilli, the extent of tuberculosis was moderately advanced in 63.5 per cent and far advanced in 36.5 per cent. In contrast, in the INH-resistant group, lesions were far advanced in 66 per cent, and in patients with multi-resistant tubercle bacilli, far-advanced lesions were noted in 83 per cent. Most patients had pulmonary tuberculosis of long duration. Of the group with sensitive infection, 52 per cent were INH-resistant; 63 per cent in the multi-resistant group and 81 per cent had long-standing disease.

Roentgenologically, pulmonary changes during specific therapy were as follows: improvement in the sensitive-infection group: 90 per cent; in the INH-resistant group: 48 per cent; in the multi-resistant group: 29 per cent. Pulmonary condition deteriorated in the sensitive-infection group: 1 per cent; INH-resistant group: 9 per cent; multi-resistant group: 22 per cent. The balance of the patients remained unchanged under treatment.

As to conversion from positive status for tubercle bacilli to negative for tubercle bacilli, parallel figures were recorded, namely: in the sensitive-infection group: 86 per cent; in the INH-resistant group: 43 per cent; in the multi-resistant group: 19 per cent.

Obviously, presence or absence of bacterial resistance has prognostic significance. The prognosis is best in sensitive bacillary infections.

In conclusion, it may be stated that bacterial resistance has a bearing not only on prognosis, but also on the extent of the disease and on the selection of specific treatment.

Differential Diagnosis of Bronchiectasis and Bronchitis*

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Bronchiectasis as a diagnostic term has been misused as a catch-all for several types of pulmonary suppuration. Its use is similar to such commonly used terms as urinary infection, congenital heart disease, or allergy. Furthermore, definitions for bronchiectasis given by the clinician, the roentgenologist, and the pathologist may differ greatly. If patients are to have the most suitable treatment, we must be specific as to type, etiology, clinical course, and associated pathological features of the various suppurative pulmonary diseases.

Bronchiectasis and bronchitis, both acute and chronic, cannot always be differentiated clinically, but characteristic bronchial deformity occurs in all three (Fig. 1). The bronchial deformity occurring in acquired bronchiectasis is saccular or fusiform; in acute and chronic bronchitis, it is cylindrical.

Bronchiectasis

Many patients with bronchiectasis give a history of pneumonia. They may be free of symptoms until there is a detrimental change in living habits. With such a change, frequent acute respiratory infections and/or exposure to bronchial irritants may produce secondary infections. They may then continue to have repeated respiratory infections, each becoming more severe. These infections are associated with cough, productive of an increasingly larger amount of purulent sputum and occasionally pneumonia. Bronchographically, saccular or fusiform dilatation is more frequently seen in the dependent bronchi (Fig. 2).

Pneumonia associated with tuberculosis is also followed by bronchographic evidence of bronchiectasis in approximately 60 per cent of patients[1] who have had moderately- or far-advanced disease (Fig. 3). Since tuberculosis is more frequently localized in the upper lobes, gravity aids bronchial drainage so that the bronchiectasis may not become symptomatic.

Evidence of destruction of muscle or fibrosis, or both, is necessary for a pathological diagnosis of bronchiectasis (Fig. 4). Destruction of

FIGURE 1—CLASSIFICATION OF BRONCHIAL DEFORMITY

1. SACCULAR OR FUSIFORM
   BRONCHIECTASIS
2. CYLINDRICAL
   ACUTE BRONCHITIS
   CHRONIC BRONCHITIS

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muscle may occur without appreciable fibrosis (Fig. 5). There is much variation in both of these processes. Usually there is also some degree of bronchitis, pneumonitis, and foci of organized pneumonia.

There is agreement clinically, roentgenologically, and pathologically, with the situation described above, in regard to the diagnosis.

Pulmonary resection is advisable in any symptomatic patient with localized bronchiectasis. When areas of bronchiectasis are not sufficiently localized to consider resection, medical treatment is unsatisfactory (Fig. 6). Patients with post-tuberculous bronchiectasis in the upper lobes are not considered for pulmonary resection unless the sputum is persistently positive for tubercle bacilli or the patient has symptoms, such as, hemoptysis or cough with purulent sputum.

Acute Bronchitis

During and following acute respiratory infections, cylindrical bronchial deformity due to acute bronchitis may have a scalloped outline, similar to the shadow cast by a string of beads (Fig. 7). It is usually seen in the dependent bronchi where elimination of secretions is poor. The deformity will disappear during an adequate medical regimen suggesting that it may be due to bronchospasm. This idea was supported by producing an exaggerated form of bronchospasm in dogs under pento-

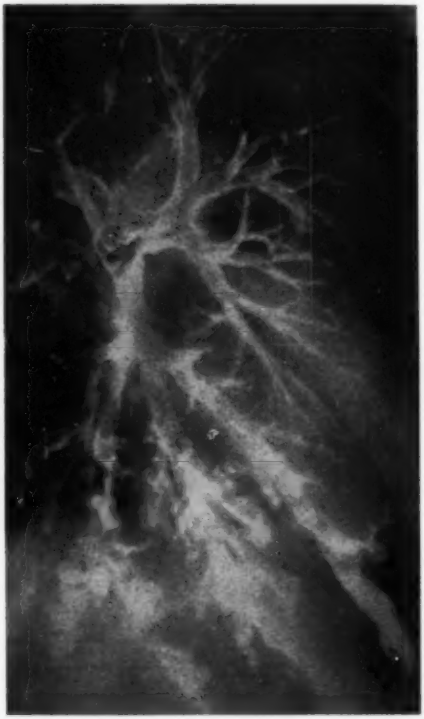

FIGURE 2: Bronchiectasis. Fusiform and saccular deformity in a patient who had pneumonia in childhood complicated by empyema requiring open thoracotomy.

barbital sodium anesthesia (Fig. 8). An intravenous injection of the bronchospastic drug, methacholine chloride, produces the same beaded appearance. The bronchi later return to normal. By obstructing the bronchial branches, bronchospasm may have a beneficial action to prevent acute infection from progressing toward the alveoli.

In acute bronchitis of less severity, this beaded appearance is seldom present (Fig. 9). As soon as the acute infection has subsided, the cylindrical deformity will disappear and the degree of return to normal will depend upon the effectiveness of treatment.

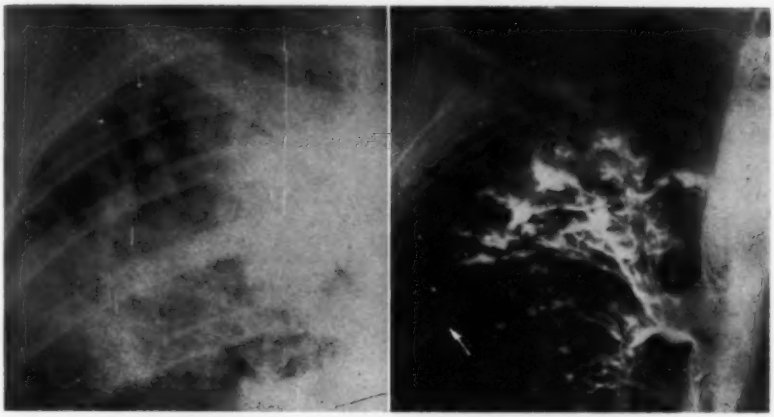

FIGURE 3A FIGURE 3B

FIGURE 3: Tuberculosis. A. Pneumonia, right upper lobe. B. Saccular and fusiform bronchiectasis with lobar contracture (see transverse fissure—arrows) fourteen months later.

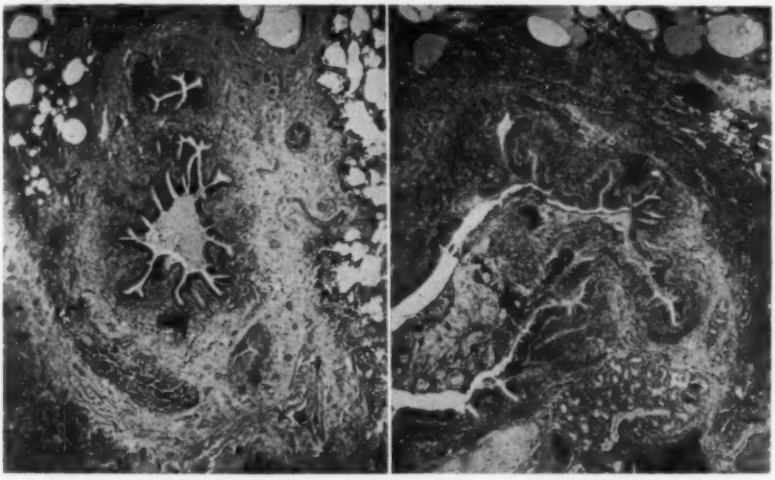

FIGURE 4 FIGURE 5

FIGURE 4: Bronchiectasis. Destruction of muscle and peribronchial fibrosis. Section from basal segment, left lower lobe, Figure 2 (40 x). FIGURE 5: Bronchiectasis. Destruction of muscle. Very little fibrosis. Moderate inflammation. Section from basal segment, left lower lobe, Figure 2 (40x).

After the infection has subsided and the deformity has disappeared, pathologic sections of the bronchi may show little or no evidence of inflammation (Fig. 10). Bronchiectasis will not be present unless there has been clinical evidence of previous pneumonia. Our experience has con-

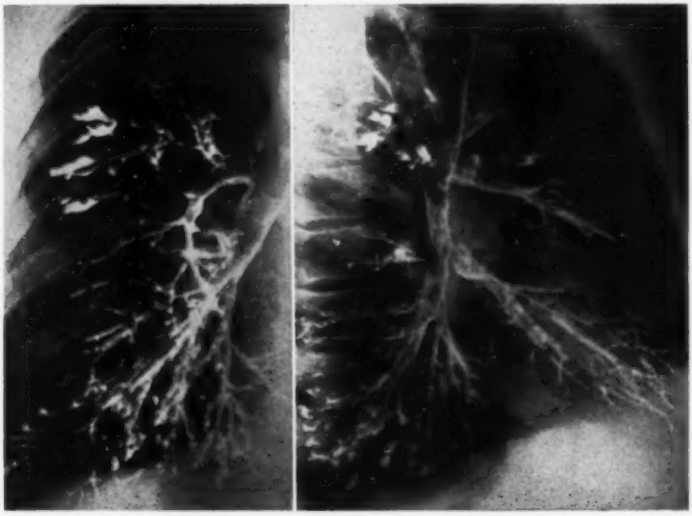

FIGURE 6A FIGURE 6B

FIGURE 6: Fusiform and saccular bronchiectasis, right upper and lower lobes. There was similar distribution of bronchiectasis in the left lung. Patient was critically ill with bilateral pneumonia during infancy. (A) PA view, (B) right lateral.

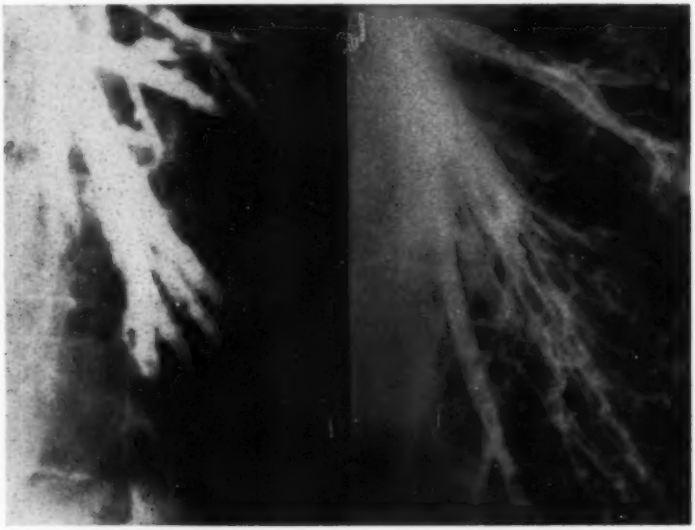

FIGURE 7A FIGURE 7B

FIGURE 7A: Cylindrical deformity with scalloped outlines, or "string-bead" deformity, basal segments, left lower lobe (posterior oblique view) due to acute bronchitis.
FIGURE 7B: Repeat bronchogram three weeks later (same view).

vinced us that it is an error to consider cylindrical bronchial deformity sufficient evidence of bronchiectasis. A repeat bronchogram should always be done before considering surgery in any patient if acute bronchitis is suspected. Patients who are susceptible to acute bronchitis should be given antibiotic therapy at the onset of any acute respiratory infection.

Chronic Bronchitis

Chronic bronchitis is a clinical entity characterized by a chronic cough productive of mucoid sputum. It is a progressive disease and involves the entire tracheobronchial tree. The etiology is probably related to inhalation of irritants, the most common being cigarette smoke. When associated with acute respiratory infections, the sputum becomes mucopurulent. Symptoms then become identical to those seen in acute bronchitis or bronchiectasis. When pneumonia is associated with the acute respiratory infections, it may vary in its location with each episode. Pneumonia is more typically seen in the upper lobes in patients with

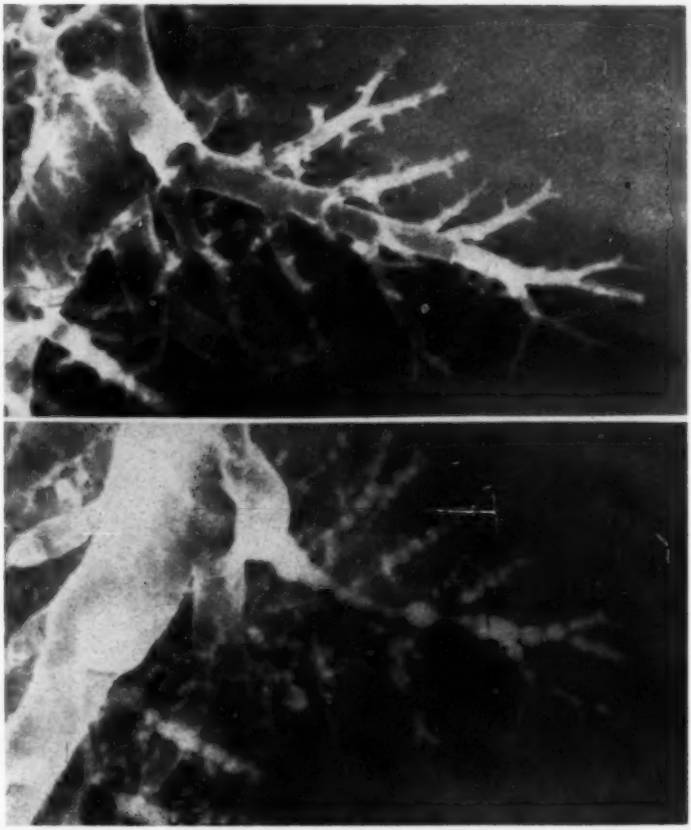

FIGURE 8A (upper): Normal bronchogram, right middle lobe, in a dog. FIGURE 8B (lower): Same as A, three minutes after intravenous bronchospastic drug. Notice cylindrical bronchial deformity with scalloped outlines, or "string-bead" appearance.

FIGURE 9A

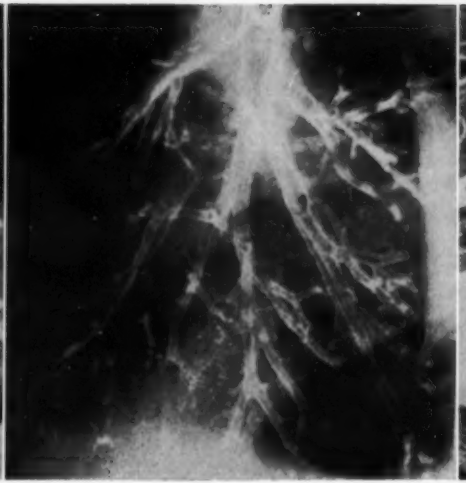

FIGURE 9B

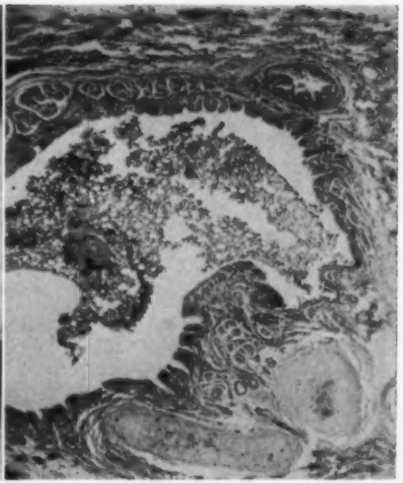

FIGURE 10

FIGURE 9A: Acute exacerbation in patient who had chronic bronchitis. **FIGURE 9B:** Repeat bronchogram, nine months later. Only minimal changes of chronic bronchitis remain. (Note especially—changes in posterior basal segment). **FIGURE 10:** Section of a posterior basal segmental bronchus resected after bronchogram, Figure 9B (40x). No evidence of bronchiectasis or bronchitis. Lumen contains injection medium.

chronic bronchitis, than with acute bronchitis or bronchiectasis. Hemoptysis may be the only presenting symptom.

A diagnosis of chronic bronchitis can be made by a careful study of a bronchogram before the usual tests reveal any significant impairment of pulmonary function. The bronchographic features* frequently described in chronic bronchitis consist of the following:[2,3,4] (a) diverticula along the larger bronchi; (b) transverse ridges in the bronchial mucosa; (c) irregularity in outline of the bronchi; (d) cylindrical dilatation or pipestem deformity; and (e) unusual variation in the diameter of the bronchi (Fig. 11). Cylindrical dilatation in chronic bronchitis usually has a generalized distribution. A roentgenogram taken 24 hours following bronchography may reveal stasis of bronchographic medium in the diseased area. This is evidence of an impaired cleansing mechanism.[2] It is due to an ineffective cough which also allows exudate to accumulate in the dependent bronchi during acute pulmonary infection. This stasis increases the severity of the inflammation, and is analogous to the almost invariable development of cystitis in a bladder that maintains residual urine. Acute bronchitis may be present at the time of bronchography

*Diagnostic features of chronic bronchitis are more readily seen in bronchograms with iodized oil containing sulfanilamide (Visciodol, E. Fougera and Company).

FIGURE 11: Bronchographic features frequently described in chronic bronchitis: (a) diverticulum, (b) mucosal cross-striations, (c) irregularity in outline, (d) pipestem deformity or cylindrical dilatation, and (e) variation in caliber of bronchi.

if the patient with chronic bronchitis has had a recent respiratory infection (Fig. 9). The degree of deformity due to acute bronchitis will depend upon the success of previous antibiotic therapy. When pneumonia is sufficiently severe, it may be followed by bronchiectasis.

Histologic sections from patients with clinical evidence of chronic bronchitis may show no evidence of inflammation. A section taken through a diverticulum will usually reveal it to be a dilated duct of a mucous gland[5] (Fig. 12). Regardless of the degree of inflammation seen histologically, clinically this bronchographic finding is diagnostic of chronic bronchitis.[6] On longitudinal section of a bronchus with cross striations, the bronchial muscle is practically confined to the mucosal projections (Fig. 13).

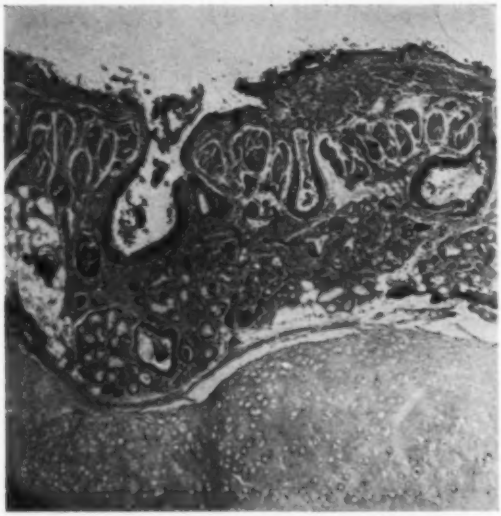

FIGURE 12: Diverticulum formed by dilated duct of a mucous gland. No inflammation.

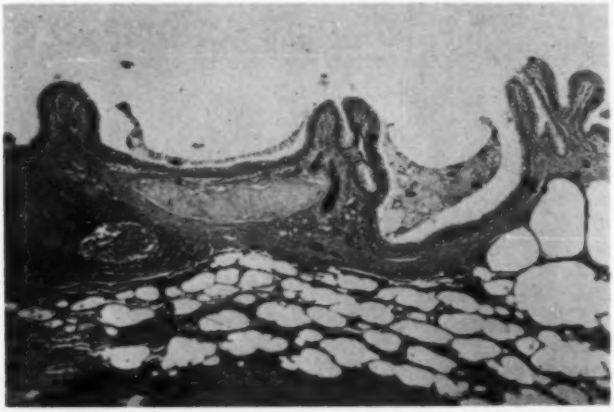

FIGURE 13: Longitudinal section of bronchus. Transverse ridges contain bundles of smooth muscle (40x).

A bronchial obstructing mechanism which may be responsible for producing the bronchographic changes characteristic of chronic bronchitis has been demonstrated by dynamic studies in a preliminary group of patients. This mechanism might also be responsible for the emphysema which is associated with the later stages of chronic bronchitis. A "check valve" mechanism has been observed previously in advanced emphysema during expiration,[7,8] but bronchial closure has recently been observed during cough in patients with chronic bronchitis before they have clinical evidence of emphysema. The closure of the bronchi is more frequently seen in the first and second order of lobar bronchi (Fig. 14). Collapse of the bronchi obstructs the flow of air from the alveoli causing a marked elevation in the expiratory airway resistance during cough. The pressure behind the obstruction may increase to a level sufficient to rupture the alveoli. The lateral pressure might also produce a dilating effect on the bronchi, as well as the ducts of the mucous glands. Further results of this study will be the subject of a subsequent report.

Treatment of chronic bronchitis should be directed toward measures to prevent secondary infection during acute respiratory infections, such as antibiotic therapy and postural drainage. Resection of the areas of cylindrical dilatation due to chronic bronchitis will not eradicate the disease. When one lobe is the site of recurrent pneumonia, pulmonary resection may be an adjunct to the medical therapy provided the extra risk of surgery can be accepted. The risk of postoperative complications following general anesthesia for any type of surgery is increased in patients with chronic bronchitis. To be forewarned by a preoperative bronchogram helps the surgeon to prevent atelectasis and pneumonia.

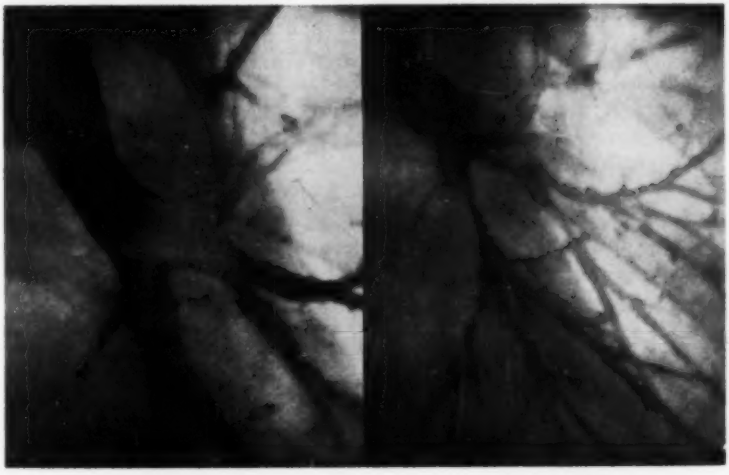

FIGURE 14A FIGURE 14B

FIGURE 14: Left bronchogram of a patient with chronic bronchitis recorded on 35 mm. film by cinebronchography. (A) Inspiration (B) Collapse of inferior lingular and left lobar bronchi during cough.

SUMMARY

1. Distinguishing bronchial deformity or dilatation occurs in bronchiectasis, as well as in acute and chronic bronchitis.

2. Bronchiectasis consists of a permanent saccular or fusiform bronchial deformity following a previous pneumonia in the same area.

3. Acute bronchitis has a reversible cylindrical deformity of the dependent bronchi following an acute respiratory infection.

4. Chronic bronchitis has diffuse bronchographic features. Preliminary clinical studies suggest that these features may be due to elevated intrabronchial pressure produced by an obstructing mechanism during cough.

RESUMEN

1. Se puede ofrecer la necesidad de distinguir la deformación y la dilatación bronquiales en bronquiectasia así como en bronquitis crónica.

2. La bronquiectasia consiste en la deformación permanente sacular o fusiforme del bronquio despues de una neumonía en esa area.

3. La bronquitis aguda hace una dilatación cilíndrica reversible de los bronquios en la region afectada.

4. La bronquitis crónica tiene características bronquiales difusas.

Los estudios preliminares sugieren que estas características pueden ser debidas a la presión intrabronquial elevada por un mecanismo de obstrucción durante la tos.

RESUMÉ

1. La distinction entre simple déformation bronchique et dilatation peut se poser tant à l'occasion d'une bronchiectasie qu'en cas de bronchite aiguë ou chronique.

2. La bronchiectasie consiste en une déformation bronchique permanente, en forme de sac ou de fuseau, suivant une atteinte pneumonique antérieure localisée à la même zone.

3. Une bronchite aiguë comporte une dilatation cylindrique réversible des bronches qui ont été l'objet d'une infection respiratoire aiguë.

4. La bronchite chronique a des tracés bronchographiques diffus. Des études cliniques préliminaires font penser que ces caractéristiques peuvent être imputables à une pression intrabronchique élevée, produite par un mécanisme d'obstruction pendant la toux.

ZUSAMMENFASSUNG

1. Unterschiedliche Deformitäten oder Dilatationen der Bronchien geschehen bei der Bronchiektasie ebenso wie bei der akuten und chronischen Bronchitis.

2. Die Bronchiektasie setzt sich zusammen aus einer permanenten Sack- oder spindelförmigen bronchialen Deformität im Anschluß an eine vorausgegangene Pneumonie des gleichen Bezirkes.

3. Die akute Bronchitis hat eine reversible zylindrische Dilatation der zugehörigen Bronchien im Anschluß an eine akute respiratorische Infektion.

4. Die chronische Bronchitis hat eine diffus ausgebreitetes bronchografisches Aussehen. Die vorläufigen klinischen Untersuchungen lassen annehmen, daß diese Eigentümlichkeiten die Folge eines erhöhten intrabronchialen Druckes sein können, der durch einen Obstruktionsmechanismus während des Husten entsteht.

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Sweat Electrolytes in Familial Pulmonary Disease*

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The etiology of chronic obstructive pulmonary emphysema is frequently uncertain, and the known laboratory procedures leading to a specific diagnosis are often unrevealing. In this paper, chronic obstructive pulmonary emphysema will be discussed with reference to sweat electrolytes and the disease entity, cystic fibrosis of the pancreas.

Pediatric literature frequently associates chronic obstructive pulmonary emphysema with classic cystic fibrosis of the pancreas. di Sant' Agnese and co-workers,[1] in 1953, revealed that abnormally high concentrations of sweat chloride and sodium were constantly associated with cystic fibrosis of the pancreas. At that time, the classic syndrome with di Sant'Agnese's findings included a strong familial incidence, pancreatic insufficiency with intestinal malabsorption, obstructive pulmonary disease, increase of sweat electrolytes, stunted growth, and early death. Recently, however, several cases of chronic pulmonary disease with a familial incidence and increased sweat electrolytes, but without pancreatic dysfunction, have been recorded as "cystic fibrosis of the pancreas."[2-6] These authors have chosen to accept this diagnosis on the basis of abnormal values for sweat electrolytes and the familial incidence of pulmonary disease.

Recently, we encountered an adult patient with severe chronic obstructive pulmonary emphysema of unknown cause. Investigation revealed several family members with chronic pulmonary disease. The findings are reported herein.

Method and Material

The values for sweat electrolytes were determined in a family of eight. Two members of the family were studied extensively in the hospital, because of their severe pulmonary disease. The sweat was collected in a specific manner: The patient was bathed and thoroughly rinsed with distilled water. He was then wrapped entirely from the shoulders down in a plastic (karoseal) bag which had previously been rinsed with distilled water. Next, the patient was placed under a cradle containing three electric lights until a minimal amount of sweat (3 to 4 cc.) formed. The duration of heating varied between 20 and 30 minutes. With sterile gloves and a sterile eye dropper, the sweat was collected and analyzed for sodium by means of the Baird or Coleman flame photometer and for chloride by means of the Cotlove colorimeter.

Several authors have reported normal values for sweat electrolytes; however, the range of normals varies a great deal. Wood and associates[6] studied 50 normal patients and found no value for sweat chloride greater than 50 milliequivalents per liter. Finch[7] found the value for sweat chloride in 40 normal persons ranged from a trace to 39 m.Eq./L. (average

*The work on which this paper is based was done in the Department of Internal Medicine, University of Minnesota Hospitals, Minneapolis, Minnesota. Acknowledgment is extended to Dr. Bruce Hatfield for his suggestions and advice.
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15.4) and the value for sodium ranged from 7.7 to 76 m.Eq./L. (average 28), while di Sant'Agnese[9] reported a range from 4 to 60 m.Eq./L. (average 27) for chloride and a range of 10 to 80 m.Eq./L. (average 52) for sodium. On the other hand, Vink[9] found the values for chloride to range from 5 to 43 m.Eq./L. (average 20) and the values for sodium to range from 5 to 56 m.Eq./L. (average 21), while Weeks[10] reported a chloride range of 6.0 to 38.4 m.Eq./L. (average 21.8), and a sodium range of 6.6 to 37.6 m.Eq./L. (average 21.8). Further work by Gochberg[12] disclosed values ranging from 10 to 35 m.Eq./L. (average 16) for chloride and from 11 to 35 m.Eq./L. (average 18) for sodium, while Hsia reported the average chloride concentration to be 19 m.Eq./L. with a standard error of 1.3, and the average sodium concentration to be 22 m.Eq./L. with a standard error of 1.9. The clinical chemistry laboratory of the University of Minnesota Hospitals has established the upper limit of normal for sweat chloride as 40 m.Eq./L. This laboratory does not routinely determine sweat sodium, so that a normal range has not been established. From the foregoing figures, the reported range of averages for sweat chloride would be approximately 15 to 30 m.Eq./L., while the approximate range for sodium would be 20 to 50 m.Eq./L. The remaining laboratory tests were carried out by standard technics with recognized standard normals.

Report of Cases

Case 1: A, a 22-year-old white farm boy, was admitted to the hospital with severe obstructive respiratory disease manifested by cyanosis, wheezing, coughing, orthopnea, nausea, vomiting, dehydration and cachexia. At the age of six months, he had been hospitalized because of severe bronchopneumonia. Since then he had had repeated winter respiratory infections which had responded poorly to treatment and had caused progressive respiratory insufficiency. At the age of 10 he had begun to manifest a dorsal kyphotic deformity of the thorax, and by the age of 18 he had obvious dyspnea on climbing one flight of stairs. Two months prior to admission, he had had a severe

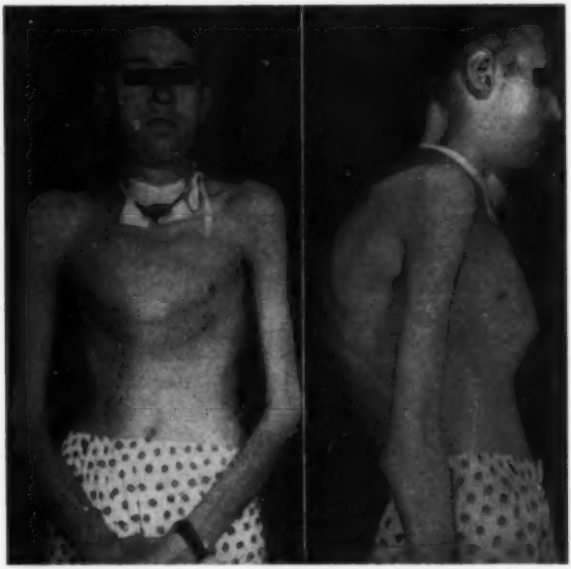

FIGURE 1 (Case 1): Retraction of lower rib cage bilaterally, dorsal kyphosis, and marked pectus carinatum.

respiratory infection with dyspnea and right heart failure. In addition to management with salt restriction, digitalis and a diuretic, he required almost continuous nasal oxygen therapy.

On examination, he (Fig. 1) weighed 110 pounds and was 68 inches tall. He was emaciated, dehydrated, dyspneic and orthopneic, with central cyanosis. The thoracic cage was deformed, with pectus carinatum, dorsal kyphosis and increased anteroposterior diameter. The diaphragm was low and moved little with respiration, while the accessory muscles of respiration were markedly hypertrophied. Expiration was prolonged over inspiration, with diminished breath sounds bilaterally and late inspiratory crepitant rales at the bases of both lungs. A grade 2, blowing systolic murmur was heard best over the apex of the heart, and the second pulmonic sound was accentuated. The abdomen appeared normal, but the terminal phalanges were moderately clubbed.

Routine examination of the blood, urinalysis, and determination of serum electrolytes and proteins gave normal results except for a carbon dioxide-combining power of 45 m.Eq./L. Results of the triple fungous and old-tuberculin skin tests were negative. X-ray film examination showed diffuse pulmonary fibrosis, inflammatory infiltration, and atelectatic changes in the right upper lobe, with areas of translucency compatible with cystic formation (Fig. 2). The electrocardiogram was suggestive of right ventricular hypertrophy and cor pulmonale. Pulmonary-function tests[12-15] (Table 1) revealed severe obstructive respiratory disease that was not relieved by bronchodilators. Studies of pancreatic function, which included the vitamin A tolerance test, determination of triolein I^{131} uptake, and duodenal aspiration for amylase, lipase and trypsin, gave normal results. The 24-hour urinary output of electrolytes, 17-ketosteroids and 17-hydroxycorticosteroids was normal. The response of the adrenal gland to stimulation with ACTH was also normal. However, a high concentration of two sweat electrolytes (sodium and chloride) was found to be present in this patient, in his younger brother (Case 2), and in two other members of the family. Administration of desoxycorticosterone acetate (DCA) did not significantly alter the concentration of sweat electrolytes.

Tenacious bronchial secretions and diminished respiratory reserve necessitated almost continuous nasal administration of oxygen. Treatment consisted of antibiotic therapy, exercises in breathing, and the establishment of a permanent tracheal stoma to permit adequate aerosol therapy and tracheal care. Two weeks after this therapy was started, the patient no longer required supplemental oxygen, and objective testing showed improved pulmonary function (Table 1).

Case 2: B, an 18-year-old brother (Fig. 3) of Case 1, also gave a history of repeated winter respiratory infections. At the age of 16, he had gradually begun to manifest mild deformities of the thorax with limited respiratory reserve which, on admission two years later, moderately restricted his physical activity.

TABLE 1—RESULTS OF PULMONARY FUNCTION TESTS AND ARTERIAL BLOOD DETERMINATIONS

	Case 1				Case 2	
	Before tracheostomy (hemoglobin 13.5 gm., respirations 30/min.)		After tracheostomy (hemoglobin 12.4 gm., respirations 28/min.)		(hemoglobin 17 gm., respirations 21/min.)	
Results of pulmonary-function tests (values in millimeters)						
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Tidal volume	311	210	350	225	653	340
Dead space	217				227	
Vital capacity	1020	4300	1470	4300	3090	4500
Maximal breathing capacity, ml./min.	9600	113,000	30,000	113,000	54,000	135,000
One-second vital capacity	300	1034	600	1250	1560	2737
Arterial blood determinations by type of inhalation						
	Room Air	40 per cent O_2	Room Air	1.5 L. of O_2/min.	Room Air	30 per cent O_2
pH of blood	7.49	7.42	7.48	7.42	7.51	7.41
Pa CO_2, mm. of Hg	58	67	46	54	31	
Conc. O_2, vol. per cent	8.8	15.6	12.3	14.9	19.6	21.1
Conc. maximal O_2, vol. per cent	18.1	18.1	17	17	22.8	22.8
Sat. O_2, per cent	49	86	78	88	87	93

TABLE 2—VALUES FOR SWEAT ELECTROLYTES IN MEMBERS OF ONE FAMILY

Family member	Sweat electrolytes, m.Eq./L.		After DCA	
	Cl	Na	Cl	Na
A (Case 1)	Av. 77 (61-100)	Av. 74 (53-101)	78	62
B (Case 2)	Av. 88 (60-117)	Av. 92 (69-119)	47	41
C (Father)	82	60		
D (Mother)	35	35		
E (Sibling)	20	35		
F (Sibling)	33	50		
G (Sibling)	20	31		
H (Sibling)	42	61		
Range of reported averages*	15 to 30	20 to 50		

*See text for normal values.

On examination, he weighed 140 pounds and was 71 inches tall. He had nasal polyps, bilateral retraction of the lower anterior part of the thoracic cage, and an increase in the anteroposterior diameter of the thorax (Fig 3). The breath sounds were slightly decreased bilaterally, but rales were not heard.

Routine and special laboratory procedures, including electrocardiographic examination, stimulation of the adrenal glands, and tests of pancreatic function, gave normal results. X-ray film examination showed an increase in the pulmonary markings compatible with early diffuse fibrotic changes (Fig. 4). Pulmonary function tests revealed moderate obstructive respiratory disease (Table 1). Bronchoscopic and bronchographic examinations gave normal results; however, biopsy of the bronchial mucosa showed chronic inflammatory changes, with dilatation of the acini and acinar ducts. A biopsy specimen from the jejunal mucosa, obtained transorally by means of a simplified biopsy capsule,[16] was found to be normal. The sweat electrolytes were abnormally increased (Table 2).

Vink[9] has made the point that sweat electrolytes are often increased in relatives of patients with classic cystic fibrosis of the pancreas. With this in mind, the remaining family members were studied briefly and three had a positive history of pulmonary dysfunction. A 12-year-old brother (H, Table 2) has had repeated winter respiratory infections associated with wheezing and dyspnea. Coughing and deep inspiration produced pain in the lower anterior part of the thorax. His symptoms have been similar to the early symptoms experienced by his older brothers (Cases 1 and 2). His

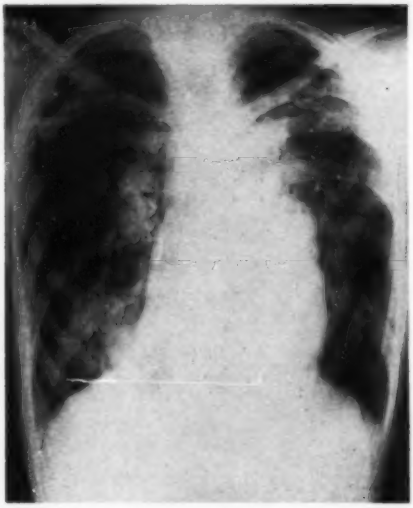

FIGURE 2 (Case 1): Diffuse pulmonary fibrosis with atelectatic and translucent areas in right upper lobe.

sweat electrolytes were increased above the reported normal range of averages for sweat electrolytes, which would suggest an abnormality (Table 2).

One sibling died in infancy of pneumonia of unknown cause.

The father, aged 54, has had recurrent winter respiratory infections with clinical evidence of reduced respiratory reserve. His electrolytes were also increased above the reported normal range of averages (Table 2). The remaining members of the family including the mother, aged 49, and three other male siblings, aged 15, 25 and 29 years, were free from respiratory dysfunction and had normal values for sweat electrolytes (Table 2).

Only one member of the family (Case 2) had allergic respiratory symptoms. His skin reaction was positive for Hormondendrum, a fungus commonly found in rural areas. However, the respiratory symptoms of allergy were minimal compared to the symptoms associated with a respiratory infection. There was no clinical evidence of intestinal malabsorption or pancreatic dysfunction in this family.

Comment

di Sant'Agnese and co-workers,[1] in their study of cystic fibrosis of the pancreas, demonstrated that the increase of sweat electrolytes in this disease was not secondary to adrenal hypofunction or to renal disease. Furthermore, salt deprivation and DCA administration did not alter the values for sweat sodium and chloride. Subsequently, they studied the incidence of abnormal values for sweat electrolytes in each family in which a case of classic cystic fibrosis of the pancreas was known to be present.[17] Of 60 family members clinically free from this disease, 14 had increased values for sweat electrolytes. Of these 14, three had generalized obstructive pulmonary emphysema and three others were unusually susceptible to respiratory infections.

Following this report of the questionable relationship of sweat electrolytes to pulmonary disease, di Sant'Agnese[2] reported on nine persons with severe chronic obstructive pulmonary emphysema associated with abnormally high concentrations of sweat electrolytes. Of the nine persons, one had steatorrhea, six had or developed slightly abnormal responses to pancreatic-function tests, and three had completely normal responses to these tests. Seven of the nine had siblings with known or suspected cystic fibrosis of the pancreas. Despite the paucity of pancreatic symptoms and findings in these nine cases, di Sant'Agnese labeled them all as cases of "cystic fibrosis of the pancreas." He put forth the idea that the diagnosis of "cystic fibrosis of the pancreas" could be made with fewer classic criteria than previously supposed. His criteria for an adequate diagnosis of "cystic fibrosis of the pancreas" consisted of (1) a positive family history, (2) evidence of pulmonary disease and (3) increase of sweat electrolytes. Other workers have agreed fully or partially with di Sant'Agnese.[3-5]

Wood and associates[5] demonstrated increase of chlorides in five of 24 patients with clinical and radiologic evidence of isolated chronic obstructive pulmonary emphy-

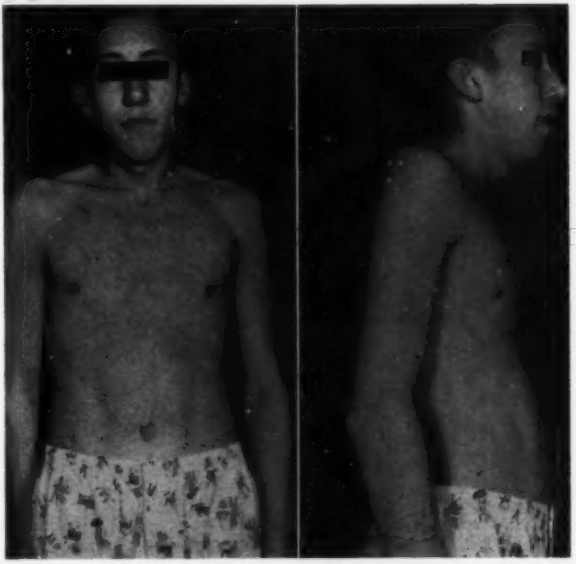

FIGURE 3 (Case 2): Retraction of lower rib cage bilaterally and dorsal kyphosis.

sema. Four of the five patients had impaired intestinal absorption of neutral fat. However, salt deprivation and DCA administration conserved the sweat chloride, and no family incidence of classic cystic fibrosis of the pancreas was stressed in their paper. Even so, these authors suggested that these five patients with increased concentrations of sweat electrolytes represented atypical forms (formes frustes) of classic cystic fibrosis of the pancreas.

In our two cases, the familial history, the abnormal values for sweat electrolytes and the pulmonary insufficiency certainly fit the criteria established by di Sant'Agnese[2] for "cystic fibrosis of the pancreas." DCA administration did not strikingly alter the loss of sweat electrolytes in Case 1, but did so moderately in Case 2. In this report, the clinical picture in Case 1 resembled that of classic cystic fibrosis of the pancreas, but more work must be done to clarify the relationship of DCA to sweat electrolytes before a more positive statement can be made.

Hsia and associates,[12] in studying the relation of allergy to changes in values for sweat sodium and chloride, found that patients with unspecified types of allergy had statistically significant increased concentrations of sweat sodium and chloride as compared with nonallergic individuals. However, the increased values reported in their paper were much lower than those seen with the classic or the atypical variety of "cystic fibrosis of the pancreas."

It becomes increasingly apparent that "cystic fibrosis of the pancreas" is a misleading term. The disease is one of generalized involvement of exocrine glands, and may be present with little or no pancreatic dysfunction. Likewise, Blackfan and Wolbach's[18] term "mucoviscidosis" is unsatisfactory, because the exocrine dysfunction is not limited to the mucus-secreting glands. Despite these facts, the authors agree with di Sant'Agnese[2] and Shwachman and associates[3] that until the etiology and pathogenesis of this disease can be clarified, the term "cystic fibrosis of the pancreas" should be retained. However, when this term is used, the great variation in the signs and symptoms of this disease entity should be kept in mind.

In trying to understand the pathogenesis of classic cystic fibrosis of the pancreas, many theories have been proposed to explain the abnormal production of mucus by the pancreas, bowels and bronchi. Gochberg and Cooke[11] pointed out the similar physiology of the sweat and mucous glands, because the nerve supply to both is mediated by acetylcholine. Therefore, they and others[19,20] have postulated that abnormal exocrine function is a result of generalized dysfunction of the autonomic system. Villee,[21] on the other hand, has expressed the view that the underlying difficulty is enzymatic. Andersen and Hodges[22] suggested that the abnormal secretory activity is secondary to intestinal malabsorption, rather than a primary defect in glandular function. Normal pancreatic function, as demonstrated, opens this theory to question. It seems more likely that the primary defect lies within the exocrine glands, with the disease entity affecting one or several systems of exocrine glands

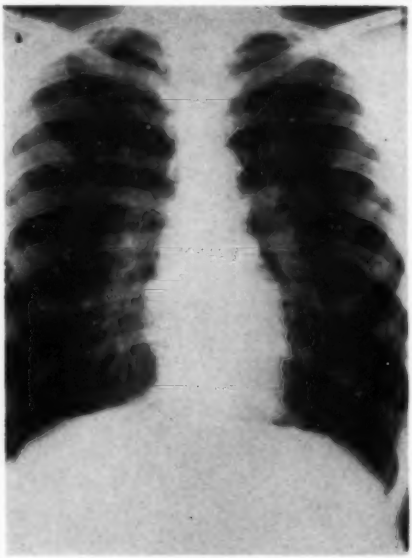

FIGURE 4 (Case 2): Increase in pulmonary markings compatible with early diffuse fibrotic changes.

throughout the body. Regardless of the etiology of cystic fibrosis of the pancreas, a better knowledge of secretory mechanisms utilized by exocrine glands will be an important tool in understanding the pathogenesis of chronic obstructive pulmonary emphysema and related conditions.

SUMMARY

An effort is made to understand the intrarelationship of sweat electrolytes, familial pulmonary disease, and the well-known disease entity, cystic fibrosis of the pancreas. The sweat electrolytes in a family of eight were analyzed, with four of the members having increased or questionably increased concentrations of sweat electrolytes. Two of the members had marked pulmonary disease, while the remaining two had histories of repeated pulmonary infections. In this paper, the two reported cases are believed to represent an atypical (forme fruste) variety of the classic disease entity, cystic fibrosis of the pancreas. It is concluded that increased knowledge of exocrine gland function will be a great help in understanding the puzzling pathogenesis of certain pulmonary diseases.

RESUMEN

Se hace un esfuerzo para comprender la relación entre los electrolitos del sudor, enfermedad pulmonar familiar, y la entidad bien conocida llamada fibrosis quística del páncreas. Los electrolitos del sudor en una familia de ocho, fueron objeto de estudio encontrándose que en cuatro de los miembros de ella, había aumento o aumento dudoso de la sconcentraciones de los electrolitos del sudor.

Dos de los miembros tenían enfermedad pulmonar acentuada, en tanto que los demás tenían antecedentes de repetidas infecciones pulmonares. En esta communicación los dos casos relatados se cree que representan una forma frustrada, atípica de la entidad clásica de la fibrosis quística del páncreas. Se concluye que sería de gran utilidad el mayor conocimiento de la función exócrina de la glándula para comprender la confusa patogenia de ciertas enfermedades pulmonares.

RESUMÉ

Les auteurs font une tentative pour comprende la relation qui existe entre les électrolytes de la transpiration, les affections pulmonaires familiales, et l'entité bien connue qu'est la fibrose kystique du pancréas. Les électrolytes de la transpiration furent analysés chez une famille de huit personnes dont quatre membres avaient une augmentation de la concentration des électrolytes de la sueur. Deux de ses membres étaient atteints d'une affection pulmonaire nette, tandis que les deux autres avaient des histoires d'infections pulmonaires répétées. Dans cette communication, les deux cas rapportés représentent, croi-on, une variété atypique (forme fruste) de l'entité classique que représente la fibrose kystique du pancréas. Les auteurs concluent que la connaissance accrue de la fonction des glandes exocrines pourra être d'un grand secours dans la compréhension de la pathogénie complexe de certaines affections pulmonaires.

ZUSAMMENFASSUNG

Es wurden Anstrengungen untenommen zwecks Verständnisses der wechselseitigen Beziehungen der Elektrolyte des Schweißes, familiärer Lungenerkrankung und der bekannten Krankheitseinheit, nämlich der cystischen Pankreasfibrose. Die Elektrolyte des Schweißes einer 8-köpfigen Familie wurde untersucht, wobei 4 von ihnen erhöhte oder fraglich erhöhte Konzentrationen der Elektrolyte des Schweißes aufwiesen. Zwei Familienmitglieder hatten eine deutliche Lungenerkrankung, und die übrigen berichteten über eine Vorgeschichte von mehrfaohen pulmonalen Infektionen. In dieser Mitteilung wird von den beiden wiedergegebenen Fällen angenommen, daß sie eine atypische Variante (forme fruste) der klassischen Krankheitseinheit, nämlich der cystischen Pankreasfibrose darstellen. Es wird mit dem Hinweis geschlossen, daß eine bessere Kenntnis der exokrinen Drüsenfunktion von großem Nutzen sei wird zum Verständnis der verwirrenden Pathogenese gewisser Lungenkrankheiten.

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SYMPTOMATIC PULMONARY DISEASE IN ARC WELDERS

The authors report a case in an arc welder of severe pulmonary insufficiency due to pulmonary fibrosis, with advanced emphysema and secondary features of polycythemia and right heart strain. The emphysema is of a very severe degree, as evidenced by the obstructive pattern of the spirogram, as well as by the marked reduction of timed vital capacity and maximal breathing capacity. Fibrosis and siderosis are evident in the lung biopsy, as well as in the thickening of the walls of the smaller blood vessels, which are associated with pulmonary hypertension. There is evidence that the explanation for the lung changes is excessive and prolonged exposure to fumes containing a combination of iron and free silica.

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Effect of Experimental Tuberculosis on Incorporation of C^{14} Acetate into Fatty Acids and Cholesterol*

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Acetate has been shown to be a primary precursor in the biosynthesis of fatty acids[1] and cholesterol.[2] Chernick *et al.*[3] and Chaikoff *et al.*[4] have demonstrated that the surviving rat as well as rabbit aorta tissues are capable of incorporating acetate 1-C^{14} into fatty acids and cholesterol. It has been reported in the case of rabbits that the lungs appear to participate actively in both the synthesis of fatty acids[5] and in the hydrolysis of glycerides.[6] Eisley and Pritham[7] have also shown the synthesis of cholesterol from labelled acetate by the aortas of hogs and turkeys. Fatty acid synthesis has been shown to occur by the addition of two-carbon units to the carboxyl end of the shorter fatty acid.[8-10] Soodak[11] and Stadtman[12] have proved that acetate is the precursor of acetoacetate and that acetoacetate takes part in the synthesis of cholesterol[13] and fatty acids.[14]

In the present investigation, we have attempted to find out the difference in the utilization of acetate, if any, by normal and tuberculous animals for the purpose of fatty acid and cholesterol synthesis.

Materials and Methods

Radioactive acetate:

Sodium acetate with the labelling in the carboxyl carbon atom was used. For the stock solution, sodium 1-C^{14}-acetate was dissolved in distilled water, volume made up to the required quantity and the radio activity of the sample determined by serial dilution and plating in planchets. The couning was done in a windowless flow counter.[15] Fatty acids and cholesterol samples in ethyl-ether solution were taken in planchets, evaporated to infinitely thin films and the radioactivity determined. The radioactivity was expressed in terms of counts per milligram of the sample per minute.

Experimental animals and mode of infection:

Guinea pigs having the same age, weight and of the same sex were given 0.2 cc. of one week old strains of H37RV tubercle bacilli in Dubos[16,17] medium subcutaneously in the hind leg.

TABLE 1—TOTAL RADIO ACTIVITY IN COUNTS PER MINUTE
(Incorporation at the end of 24 hrs.)

Tissues	Normal		Tuberculous	
	Fatty Acids	Cholesterol	Fatty Acids	Cholesterol
Liver	9170	1418	3900	1630
Lung	10000	1260	4800	1300
Kidney	8540	275	2160	266
Heart	200	50	188	130
Spleen	150	85	120	140
Adrenals	440	100	350	180

*V. Patel Chest Institute, University of Delhi

Administration of acetate and collection of tissues:

Between the fourth and fifth weeks after inoculation with tubercle bacilli a tracer dose of radioactive sodium acetate with an activity of 1.5×10^6 counts per ml. per minute was injected intraperitoneally to one animal each in both the un-infected control and the tuberculous group.[18] After the specified time, the animals were sacrificed and the tissues such as liver, lung, kidney, heart, spleen and adrenals were removed. These tissues were examined histologically and bacteriologically to make sure of the pathogenicity of the infection.

Extraction and fractionation of the lipids:

The weighed tissues were homogenized, using 5 volumes of ethanol per volume of the tissue. The total lipids were extracted by successive portions of ethanol, ethanol-ethyl ether (1:1) mixture and finally ethyl-ether for 30 minutes each on a water bath and the extracts decanted through filter paper. The total extracts were freed from ethyl-ether by vacuum distillation and the volume reduced to about 10 ml. The total lipids in alcohol were then saponified by adding excess of alcoholic potassium hydroxide and refluxing on water bath for six hours. The contents were cooled, about 100 ml. distilled water added and the unsaponified portions representing mainly cholesterol were extracted repeatedly with ethyl ether. The potassium soaps left over were acidified completely with $5NH_2SO_4$ and the fatty acids thus liberated were extracted with ethyl-ether. The ethereal extracts of both the cholesterol and fatty acids were washed several times with distilled water to remove traces of alkali and mineral acids adhering. The free fatty acids and cholesterol solutions in ether were dried over anhydrous sodium sulphate.

Determination of fatty acids and cholesterol:

The total fatty acids content in each organ was determined by the method of Stoddard and Drury[19] and Man and Gildea.[20] For the determination of total cholesterol content, Reinhold and Shiel's modification[21] of Myers-Wardell method[22] in which Liebermann-Burchard reaction with acetic anhydride and concentrated sulphuric acid is used for the development of color, was employed.

TABLE 2—*AD LIBITUM GROUP*

FATTY ACID CONTENT OF THE TISSUES EXPRESSED IN TERMS OF MG. OF FATTY ACIDS PER GRAM DRY WEIGHT OF THE TISSUES AND THE SPECIFIC ACTIVITY IN COUNTS PER MG. OF FATTY ACID PER MINUTE

	Animals Sacrificed Three Hours after Giving Radioactive Acetate			
	Normal		Tuberculous	
	Fatty acids	Specific Activity	Fatty acids	Specific Activity
Liver	39.6±1.3	178±20	34.0±1.8	72±7
Lung	34.1±0.9	165±32	24.0±1.2	50±4
Kidney	38.9±1.4	158±28	33.7±1.1	69±5
	Animals Sacrificed 24 Hours after Giving Radioactive Acetate			
	Normal		Tuberculous	
	Fatty acids	Specific Activity	Fatty acids	Specific Activity
Liver	39.8±1.2	265±13	28.7±1.9	95±12
Lung	30.6±0.9	209±14	21.7±0.6	68±10
Kidney	36.8±2.4	167±26	29.5±1.0	72±8

Results and Discussions

As a preliminary experiment, all the important tissues such as lung, liver, kidney, spleen, heart and adrenals were taken 24 hours after administration of labelled acetate and used for the estimation of fatty acids and cholesterol as well as their radioactivity.

The results are given in Table 1.

The significant difference noticed in normal and tuberculous guinea pigs in the incorporation of acetate for the synthesis of fatty acids by liver, lung and kidneys was appreciable. Hence it was contemplated to focus more attention on these three organs and conduct further investigations.

Two series of experiments were performed to confirm the above findings. In the first series the experimental and uninfected control groups were given the usual diet and allowed to eat and drink *ad libitum*. In the second set both the groups of animals were given isocaloric balanced diet containing carbohydrates, proteins, fats, vitamins and mineral salts. In both the series all the animals were housed individually in wide-mesh-screen-bottom metal cages provided with water and food dishes which were cleaned and replenished daily. The animals were sacrificed three hours and 24 hours after the administration of radioactive acetate. Lung, liver and kidneys were removed and a portion from each tissue examined histopathologically. The extraction, separation and estimation of the fatty acids and cholesterol and the determination of the radioactivity were performed as described earlier. The average results of six experiments on the *ad libitum* group are given in Table 2 whereas those on the group maintained on balanced isocaloric diet are given in Tables 3 and 4.

On comparing the results in Table 1 from normal and tuberculous guinea pigs an appreciable difference in the fatty acid synthesis from sodium acetate I-C^{14} is noticeable in the case of liver, lung and kidneys.

Table 2 represents the results of investigations on an elaborate study of lungs, liver and kidneys only. The control and experimental animals were allowed to eat and drink *ad libitum* in this series of experiments. The tracer dose of acetate was 1 ml. having an activity of 1.5×10^6 counts per ml. per minute. The animals were sacrificed three hours and 24 hours after the administration of acetate. The utilization of sodium acetate 1-C^{14} was about half in the tuberculous animals as compared to normal uninfected controls in liver and kidneys and to about one third in lungs.

Tables 3 and 4 represent the results of the same set of experiments as in Table 2, the only difference being pair feeding with isocaloric balanced diet was adopted instead of *ad libitum* feeding. Here, also, the results are in agreement with those of Table 2.

All the three sets of experiments prove that there is a definite difference in the utilization of acetate by normal and tuberculous guinea pigs for the purpose of fatty acid synthesis.

A decrease in the amount of total fatty acids expressed in terms of mg. per gram dry weight of the tissues in lung could be noticed from Table 3 in the case of infected guinea pigs as compared to normal controls. In liver and kidneys this decrease is not so significant as in the case of lung. This finding is in agreement with those of Patnode and Hudgins[23] who have reported 60 to 70 per cent reduction in the glycerine fatty acids in lungs of infected rabbits. In our findings the reduction of fatty acids is only 30 per cent in infected guinea pigs as compared to uninfected controls. Disturbance in the activity of liver lipases including both increase and decrease from normal have been described by many authors.[24-26] Evidence is accumulating that the lipase

TABLE 3—*PAIR FED GROUP*

FATTY ACIDS CONTENT OF TISSUES EXPRESSED IN TERMS OF MG. OF FATTY ACIDS PER GRAM DRY WEIGHT OF THE TISSUES AND SPECIFIC ACTIVITY IN COUNTS PER MG. OF FATTY ACIDS PER MINUTE

Animals Sacrificed Three Hours after Giving Radioactive Acetate				
	Normal		Tuberculous	
	Fatty Acids	Specific Activity	Fatty Acids	Specific Activity
Liver	36.3±0.8	142±25	28.1±1.4	71±5
Lung	34.2±1.0	167±27	17.2±0.7	45±3
Kidney	35.7±1.1	141±15	31.6±2.1	69±10
Animals Sacrificed 24 Hours after the Administration of Radioactive Acetate				
	Normal		Tuberculous	
	Fatty Acids	Specific Activity	Fatty Acids	Specific Activity
Liver	36.8±0.9	173±12	25.1±1.8	63±5
Lung	29.1±0.4	175±18	19.3±1.2	59±8
Kidney	33.9±1.4	185±8	29.7±0.8	67±7

TABLE 4

CHOLESTEROL CONTENT OF TISSUES, EXPRESSED IN TERMS OF MG. PER GRAM DRY WEIGHT AND RADIOACTIVITY IN COUNTS PER MG. CHOLESTEROL PER MINUTE

(The Average Values of *ad libitum* and Pair Fed Group of Animals)

	Animals Sacrificed Three Hours after the Administration of Radioactive Acetate			
	Normal		Tuberculous	
	Cholesterol	Specific Activity	Cholesterol	Specific Activity
Liver	12.2±0.4	136±26	11.4±0.3	110±24
Lung	4.1±0.2	138±18	4.2±0.3	132±11
Kidney	7.2±0.6	145±15	7.8±0.4	117±13
	Animals Sacrificed 24 Hours after the Administration of Radioactive Acetate			
	Normal		Tuberculous	
	Cholesterol	Specific Activity	Cholesterol	Specific Activity
Liver	1.2±0.7	175±7	11.4±0.5	155±23
Lung	4.0±0.2	202±15	4.2±0.2	154±9
Kidney	5.4±0.3	176±20	5.2±0.4	158±12

activity has an effect on lipid storage under normal and diseased conditions. The possible mechanism involved in the reduction of fatty acid content in tissues is not clear even though a definite decrease in the synthesis of fatty acids from acetate is evident from the experimental data presented.

The wet weight of the tuberculous tissues, especially lung and liver, was found to be higher in infected guinea pigs as compared to normal ones. An increase in weight of 26.9±14.0 per cent in liver, 24.8±4.3 per cent in the lungs and 8.2±2.7 per cent in kidneys was observed in infected guinea pigs. This increase in weight of the lungs of infected guinea pigs finds an interesting correlation in the studies of experimental tuberculosis in mice.[27] Our findings are in perfect agreement with the reports of Patnode and Hudgins[23] and Gupta and Sen.[25]

It is unlikely that malnutrition or unequal consumption of calories were responsible for the observed effects in our present studies, since isocaloric pair feeding with balanced diet has given almost parallel results with respect to incorporation of acetate as those of *ad libitum* feeding series. The entire lung, liver and kidneys were used for investigations since different lobes or parts may differ markedly in their lipid and moisture content and hence may not give typical results.

Further work in connection with enzymatic changes concerned with fatty acid synthesis and utilization in normal and tuberculous guinea pigs, is in progress.

SUMMARY

Acetate utilization for the purpose of fatty acid synthesis is found to be decreased in tuberculous guinea pigs as compared to normal ones. This difference was more pronounced in the lungs than in any other organ. *In vivo* experiments showed this difference of acetate utilization for fatty acid synthesis. The experiments with pair fed animals receiving isocaloric balanced diet also gave identical results. No appreciable change in the cholesterol synthesis was noticed in either case.

RESUMEN

La utilización del acetato para la síntesis de ácidos grasos se ha encontrado que decrece en los cuyes tuberculosos en comparación con los normales. Esta diferencia es mas pronunciada en los pulmones que otros órganos. Los experimentos *in vivo* demostraron esta diferencia de la utilización del acetato para la síntesis de ácidos grasos. Los experimentos con pares de animales recibiendo dieta isocalórica equilibrada, produjeron idénticos resultados. No se encontró cambio notable en la síntesis del colesterol en ningún caso.

RESUMÉ

L'utilisation d'acétate pour produire la synthèse des acides gras se trouve être diminuée chez les cobayes tuberculeux par comparaison avec les cobayes normaux. Cette différence a été plus prononcée dans les poumons que dans tout autre organe. *In vivo* les expériences montrèrent cette différence dans l'utilisation de l'acétate pour la synthèse des acides gras. Les expériences sur des animaux recevant un régime isocalorique équilibré donna également des résultats identiques. Aucune modification appréciable dans la synthèse du cholestérol ne fut notée.

ZUSAMMENFASSUNG

Die Ausnutzung von Essigsäureester zum Zweck der Synthese von Fettsäuren erwies sich bei tuberkulösen Meerschweinchen im Vergleich zu normalen Versuchstieren herabgesetzt. Diese Differenz war in den Lungen stärker ausgeprägt als in allen anderen Organen. Es waren *in vivo*-Experimente, die diese Differenz der Ausnutzung von Essigsäureester für die Fettsäure-Synthese zeigte. Die Versuche mit Paaren von Tieren, die aufgezogen waren mit einer isokalorisch ausgewogenen Diät, ergaben identische Resultate. In keinem Fall wurden nennenswerte Abweichungen in der Cholesterol-Synthese bemerkt.

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The Circulation of the Primary Lobule of the Lung

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In studying the circulation of the lung several methods have been employed in the past including injection methods with India ink and blue gelatin. In this study we used corrosion models for investigating the terminal arterial (arteriolar, precapillary and capillary) structures in the primary lobule.

This method has certain advantages as well as disadvantages. It is an advantage to see the structures in their natural relationship to other structures, their configuration and size. Since the histological features, however, can not be studied and the size of a structure is not absolutely reliable, as it may vary with the pressure employed during the injection, some of the structures cannot be identified with certainty. This is a disadvantage. An investigator experienced with this method of study does not have particular difficulty in recognizing the different components of the primary lobule but it may be difficult to demonstrate it photographically.

It is rather difficult, however, to classify blood vessels into their precise category such as arteriole, precapillary or capillary. In this study, therefore, a particular term for a vessel was used when we felt that the location and size of the vessel justified its usage.

By the term primary lobule we mean the ensemble of alveolar duct, atria, air sacs and air cells (alveoli) as defined by Miller*[1]

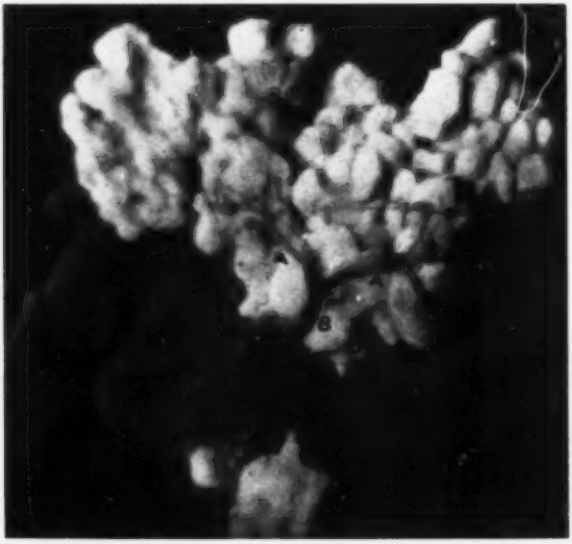

FIGURE 1: An arteriole measuring 0.042 mm. in diameter (B) divides into two alveolar duct precapillaries. (A) Both of these subdivide into a capillary network while still coursing along the alveolar duct. (Magnification 60x)

*"Air cells" is according to the English nomenclature. We shall use the term alveoli because it is commonly used on this continent.

There is general agreement that the pulmonary artery and the bronchial tree have a close relationship throughout their subdivisions.[1,7,8] It has also been shown that the capillary network of the lung is extensive and that there are numerous anastomatic channels between the terminal vessels of the pulmonary artery, vein and the bronchial arteries.[4]

Concerning the circulation of the primary lobule it was assumed that the arteriole running parallel to the respiratory bronchiole continues to divide along the pattern of the branches of the primary lobule.[1,7] On reaching the level of the air sacs the vessel, by now a precapillary, comes to lie between air sacs and gives off capillaries to the respective alveoli. Each alveolus therefore, has a capillary network of its own, somewhat along the pattern of the renal glomerulus.

The purpose of this paper is to present evidence that in the primary lobule the pattern of close relationship between the vessels of the pulmonary artery and the bronchial tree is discontinued. It will be shown that beyond the vessel running parallel to the alveolar duct there are only the capillary networks of the alveoli.

Methods

Lungs were injected with Vultex Moulage† using a modified method of Lieb.[3]

In earlier studies Neoprene was used but we found Vultex Moulage superior. It has the advantage of being miscible with water and thus can be diluted as conditions require. Vultex Moulage appears to be also more stable and does not deteriorate when mounted on slides.

Normal human lungs were used* and during their removal care was taken to leave the stems of the pulmonary artery and veins and of the bronchus as long as possible. The lung was rinsed with physiological saline solution by cannulating the pulmonary artery and allowing the

†Obtained from General Latex and Chemicals Ltd., Verdun, Quebec.
*From the necropsy service of the Vancouver General Hospital.

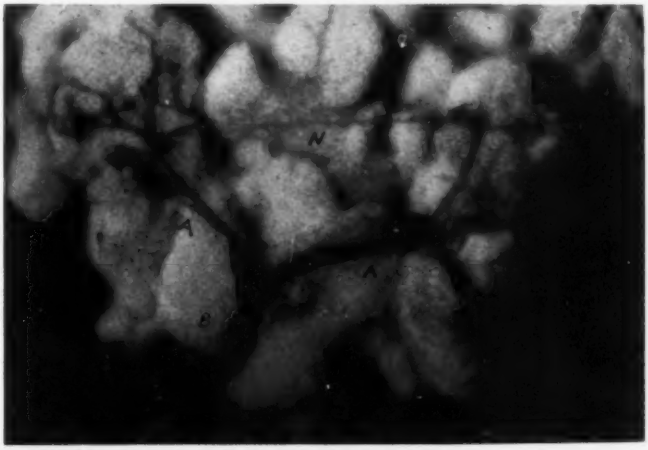

FIGURE 2: Same as Fig. 1. Note the anastomosis (N) between the capillary networks of adjacent primary lobules (Magnification 120x)

solution to run in from a height of about 120 cm. The flow was interrupted occasionally to avoid overdistension of the lung. The rinsing was continued until the parenchyma assumed a greyish or greyish pink color. As much as possible of the fluid was removed by gently compressing the lung and forcing the fluid out through the pulmonary vein. A considerable quantity of fluid also oozed out through the pleura.

The pulmonary artery was then injected with blue Vultex Moulage using the same system as was used for the rinsing. The lung was frequently inspected for leaks, which were then clamped and tied. A stubborn leak could sometimes be sealed by congealing the latex by application of concentrated hydrochloric acid.

The pressure with which the lung was injected was adjusted according to the ease of flow and the presence or absence of leaks. As a rule the injection fluid was permitted to run from a height of 120 cm., but if conditions were favorable, extra pressure was applied by forcing air into the bottle.

Figure 3A

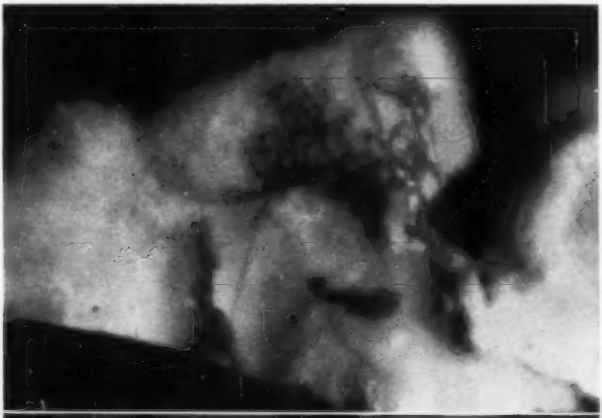

Figure 3B

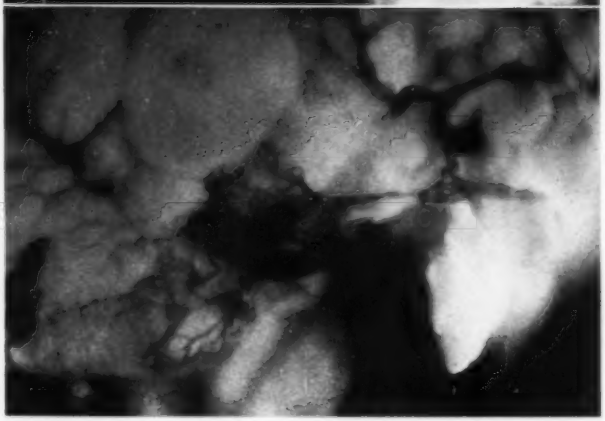

FIGURE 3A and 3B: The capillary network of one alveolus continues on to the adjacent alveolus. In Fig. 3A (upper) a rather small capillary feeds the rich network. (Magnification 120x)

To inject the pulmonary vein red Vultex Moulage was used. After the blood vessels had been adequately filled the bronchial tree was injected with white Vultex Moulage.

After completion of the injection the cannulae were tied and severed. The preparation was immersed in concentrated hydrochloric acid until all tissues had been digested. This usually required from 48 to 72 hours. The model was then thoroughly washed in water following which it was ready for study.

Suitable pieces of the model were studied and dissected under a dissection microscope. Slides were prepared according to the method of Duff.[5] Measurements were made by the use of a calibrated grid located in the eyepiece of the microscope.

Observations

Dissections of the models showed, as described by Miller and Hayek[1,7] that there is a close relationship between the pulmonary artery and the bronchial tree throughout its subdivisions. Our dissections, however, revealed that this relationship is discontinued when the pulmonary arteriole reaches the alveolar duct of the primary lobule. At this point the arteriole (B, Fig. 1 and 2) breaks up into precapillaries (A, A.) which after travelling a short distance break up into capillaries, forming a network over the alveoli.

Anastomoses between different sections of the capillary network and between capillaries feeding the network were observed frequently. One dissection demonstrated an anastomosis between the capillary networks of adjacent primary lobules (N, Fig. 2).

Close inspection of the capillary network revealed that it is not confined to one alveolus but continues on from one alveolus to another (Fig. 3).

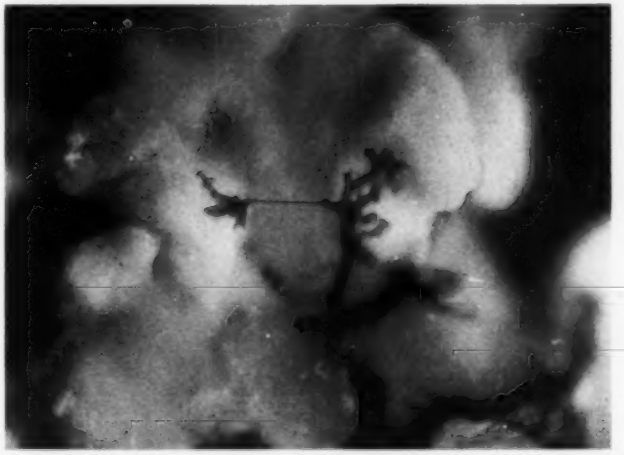

FIGURE 4: A capillary takes its origin from a capillary network of an alveolus and proceeds to another alveolus to start another network. (Magnification 120x)

A capillary may take its origin from a capillary network of an alveolus and proceed to another alveolus, sometimes a considerable distance away to start another network (Fig. 4).

A finding of considerable interest is the fact that not all capillary networks of the alveoli are formed from branches of an alveolar duct precapillary. Thus a vessel considerably larger than an alveolar duct precapillary measuring from 0.07 mm. to 0.20 mm. in diameter, while running along in a sulcus between alveoli toward the periphery may give off numerous capillary sized vessels to the adjacent alveoli (Fig. 5).

In some instances a capillary travels a considerable distance before it attaches itself to an alveolus to form a capillary network. The capillary may bifurcate and supply two adjacent alveoli (A, Fig. 6) and the network can be seen to spread from alveolus to alveolus. Sometimes more than one capillary feeds the network of an alveolus (B, Fig. 6). Rich anastomoses between the vessels given off from the mother vessel have been observed (Fig. 6 and 7).

Alveoli immediately adjacent to a larger vessel may receive several vessels which proceed to form the capillary network and these vessels may come from different branches of the larger vessel (Fig. 8).

The feeding capillaries for the network vary in size from 0.014 mm. to 0.021 mm. in diameter. The capillaries of the alveolar network measure less than 0.014 mm.* in diameter and by their anastomoses form a net consisting of a multitude of even hexagonal spaces which measure approximately 0.02 mm. square.

Discussion

Our studies have shown that the capillary network is not necessarily confined to one alveolus but may continue on to the adjacent alveolus. This phenomenon has been observed frequently. There are anastomoses between different sections of capil-

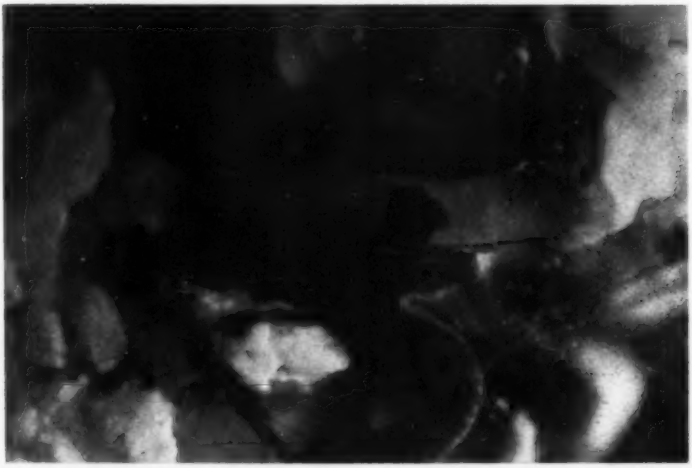

FIGURE 5: Arterioles measuring from 0.07 to 0.2 mm. in diameter give off numerous capillary sized vessels to the adjacent alveoli. A capillary may bifurcate and supply two adjacent alveoli (A). (Magnification 120x)

*One division in the calibrated grid is equal to 0.014 mm.

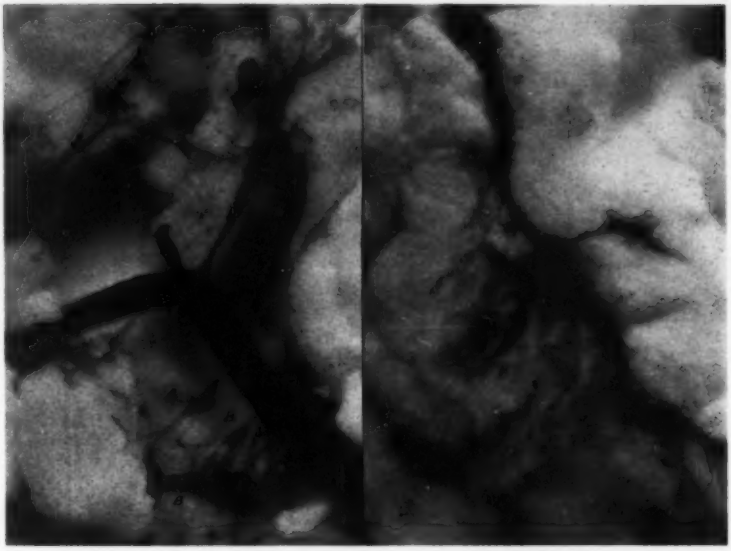

FIGURE 6 FIGURE 7

FIGURE 6: More than one capillary may feed the network of an alveolus. Note anastomoses between the various vessels. (Magnification 120x) FIGURE 7: An arteriole proceeding to the periphery supplies adjacent alveoli with capillary networks. Numerous capillary sized anastomotic channels bridge across the sulcus. (Magnification 120x)

lary networks and also between the capillaries feeding the networks. We use the name feeding capillaries in this instance because they do not fit the description of the precapillary sinus described by Hayek.[7]

Because of the numerous anastomatic channels the effect of an occlusion of a small peripheral artery in the lung can thus be overcome. This may explain the scarcity of residual ill effects from small emboli to the lung.

FIGURE 8: Alveoli immediately adjacent to a large arteriole (.084 mm. in diameter) receive several vessels which proceed to form the capillary network. The capillaries of the alveolar network measure less than 0.014 mm. in diameter. (Magnification 120x)

The small size of the capillaries in the alveolar network permits adequate exposure of the red blood cells to the alveolar membrane. Since a capillary measures less than 0.014 mm. in diameter it implies that not more than two red blood cells can travel side by side through such a capillary. Each red blood cell is, therefore, exposed to at least one alveolar surface during its journey through the capillary.

It must of course be understood that the measurements as obtained from these models are not necessarily identical with those of the living lung. The smaller vessels of the lung must enjoy a tremendous elasticity and be capable of changing their diameter as physiological conditions require. Nevertheless, these mesaurements give us comparative values of the vessels of the primary lobule of the lung.

SUMMARY

The following observations were made from microscopic dissections of corrosion models of human lungs:

1. Distal to the alveolar duct of the primary lobule there are no further vessels which can be identified as subdivisions of the pulmonary artery, except the capillary network of the alveoli.
2. There are rich anastomoses between the vessels feeding the capillary network and between different sections of the network itself.
3. A capillary network is not necessarily confined to one alveolus, but continues on from one alveolus to another.
4. Alveoli adjacent to vessels proximal to the alveolar duct precapillary have their alveolar capillary networks formed directly from branches of these vessels.
5. The capillaries of the network measure less than 0.014 mm. in diameter which implies that every red blood cell passing through these capillaries has at least one side exposed directly to the alveolar surface.

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*Provided from N.R.C. Canada Grant T-7.

RESUMEN

Mediante la disección microscópica de modelos de los pulmones humanos, obtenidos por corrosión, se han hecho las siguientes observaciones:

1. Distalmente al ducto alveolar del lubulillo primario no hay mas vasos que puedan identificarse como subdivisiones de la arteria pulmonar con excepción de la red capilar alveolar.
2. Hay anastomosis muy ricas entre los vasos que surten la red capilar y entre las diferentes secciones de la red misma.
3. Una red capilar no está limitada necesariamente a un alveolo, sino que se continúa de uno a otro alveolo.
4. Los alveolos adyacentes a los casos proximales al ducto alveolar precapilar, tienen sus redes alveolares capilares formadas directamente por ramas de esos vasos.
5. Los capilares de la red miden menos de 0.014 mm. de diámetro, lo que significa que cada eritrocito que pasa a través de esos capilares tiene cuando menos uno de sus lados expuesto a la superficie alveolar.

RESUMÉ

Les observations suivantes furent faites d'après des dissections microscopiques de poumons humains:

1. Au-delà du conduit alvéolaire du lobule primaire, il n'y a plus de vaisseaux qui puissent être identifiés comme subdivisions de l'artère pulmonaire, à part la trame capillaire des alvéoles.
2. Il y a des anastomoses importantes entre les vaisseaux nourrissant la trame capillaire et entre les différentes sections de la trame elle-même.
3. Un réseau capillaire n'est pas nécessairement confiné à une seule alvéole, mais se continue d'une alvéole à l'autre.
4. Les alvéoles adjacentes au vaisseau proche du conduit alvéolaire précapillaire ont leur trame alvéolo-capillaire constituée directement des branches de ces vaisseaux.
5. Les capillaires du réseau mesurent moins de 0mm.014 de diamètre, ce qui implique que chaque hématie passant à travers ces capillaires a au moins un côté exposé directement à la surface alvéolaire.

ZUSAMMENFASSUNG

Die folgenden Beobachtungen wurden an mikroskopischen Schnitten von Korrosionspräparaten menschlicher Lungen gewonnen.

1. Distal zu den Alveolargängen eines primären Lobulus finden sich keine weiteren Gefäße, die sich als Unterteilungen der Pulmonal-Arterie erkennen lassen, außer dem kapillaren Netzwerk der Alveolen.

2. Es gibt reiche Anastomosen zwischen den das kapillare Netzwerk versorgenden Gefäßen und den verschiedenen Bezirken des Netzwerkes selbst.

3. Ein kapillares Netzwerk ist nicht notwendig auf eine Alveole beschränkt, sondern setzt sich von einer Alveole zur anderen fort.

4. Diejenigen Alveolen, die an Gefäße proximal zum ductus alveolaris präcapillär angrenzen, bilden ihr alveoläres kapillares Netzwerk direkt von Verzweigungen dieser Gefäße.

5. Die Kapillaren des Netzwerkes messen weniger als 0.014 mm im Durchmesser was besagt, daß jedes rote Blutkörperchen, das diese Kapillaren durchströmt, wenigstens auf einer Seite direkt der Oberfläche der Alveolen ausgesetzt ist.

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PHYSIOLOGIC ANTICOAGULATING SYSTEM AND EXPERIMENTAL PRETHROMBOTIC CONDITION OF THE ORGANISM

Experimental investigations disclosed that in the organism of animals, preservation of the circulating blood in a liquid state is dependent upon the function of the neurohumoral anticoagulating system. The principle of action of this system consists in the following: in case of appearance in the circulating blood of a thrombin concentration endangering the organism's life, the chemoreceptor vascular apparatus sends an impulse along the reflex arc, as a result of which there occurs an effector act characterized by ejection into the blood of substances preventing blood coagulation. Heparin and heparin-like agents and activators of the fibrinolytic process belong to these substances. Further detailed investigation of the nature and function of the physiologic anticoagulating system effected on more than 3,000 animals divulged that the reflex arc of the anticoagulating system circuits at the level of the medulla oblongata and that the exclusion of the vegetative nervous system provokes dysfunction of the physiologic anticoagulating system. It was also ascertained that the reticuloendothelial system takes part in the humoral effector act of the referred to system. A diet enriched with animal fat and cholesterol causes in the animals a depression of function of the physiologic anticoagulation system after several months of the experiment.

In experimental prethrombotic condition in the animal's organism, there is noted an augmented concentration of fibrinogen, a sharp drop of the fibrinolytic activity of the blood and an increase of plasma tolerance to heparin. In the prethrombotic condition caused by depression of the anticoagulating system, a preventive effect was obtained with heparin and trypsin inhibitor from soy beans, whereas in prethrombotic condition caused by depression of the vegetative nervous system, by antithrombin VI.

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A County-Wide School Certification Program for Tuberculosis Control: Newton County, Missouri

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The tuberculin test is now recognized as a major case-finding tool in tuberculosis. The test has become more valuable in recent years because of the decrease in the number of positive tuberculin reactors, and it will grow in importance as a valuable case-finding tool as the infection rate declines. The future cases of tuberculosis will occur in persons who harbor tubercle bacilli in their bodies and who have a positive tuberculin skin test. There are many in Missouri who feel that in the future tuberculin testing of all individuals, with follow-up of the reactors, will be the major method of control if tuberculosis is ever to be eradicated.

At the present time, tuberculin testing on a mass scale is not feasible. However, tuberculin testing of school children is a real possibility; and, if done on a continuing basis with proper education and follow-up, it can lead to eventual tuberculin testing of all or most of the population and form the basis for a practicable case-finding program.

At the present time, at least 11 states have a school tuberculin testing program in progress. They are using the American School Health Association certification plan. This program of school certification creates and stimulates the interest of the public and physicians in tuberculin testing, case-finding, and tuberculosis control. The associated promotion, education, and follow-up can lead to total community or county case-finding, as well as eliminate the tuberculosis problem in the schools.

In November of 1959, Missouri put into operation the first phase of a pilot program of tuberculin testing in the schools. The standards set forth by the American School Health Association Committee on Tuberculosis were used in forming the requirements for certification. To qualify for a class "A" certificate, 95 through 100 per cent of the school children and all school personnel had to be tuberculin tested and read. For a "B" certificate, 80 through 94 per cent of the school children and all personnel had to be tuberculin tested and read. To remain certified, all non-reactors found at the original testing must be retested at least every two years, preferably every year; and, once a year, new pupils not previously tested or without a record of a definite positive to the intermediate Mantoux test dose must also be tested.

The Missouri Sub-Committee also recommended that all positive reactors have a chest x-ray film immediately, plus a physical examination if indicated, with reference to tuberculous lesions in other parts of the body which might be discharging tubercle bacilli. Students and personnel

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with an abnormal chest x-ray film should have a thorough examination to determine if active tuberculosis is present. Anyone in the contagious stage should be removed from school until adequate treatment is administered and the danger of contagion removed.

After the initial one, x-ray films should be taken annually for life, beginning at the age of 12 years, or as often as recommended by the family physician. All immediate household contacts of positive reactors found in the schools were to be skin tested, and the positive reactors found were to have a chest x-ray film and a physical examination. In addition, the Sub-Committee recommended drug therapy with isoniazid in the dosage of 5 to 8 milligrams per kilogram of body weight per day for one year in children five years of age and under with positive tuberculin and for all known recent converters.

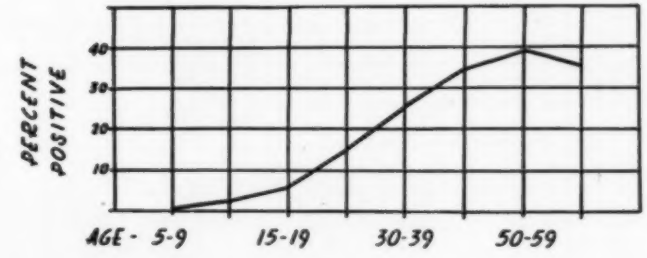
Newton County in Missouri was selected for a pilot study to determine policies and procedures that could be applied to a state-wide program. Newton County is located in southwestern Missouri and has an area of 622 square miles with a population of 29,000. There are 48 schools in the county, with approximately 6400 students and 437 school employees. Lead and zinc mining has been carried on in this county for more than 100 years. The tuberculosis death rate for this county has been high; and, when a tuberculosis problem was discovered in a school in 1959, a request for a county-wide school testing program was made.

Materials and Methods

The first step in organization was the appointment of the Missouri Sub-Committee of the Committee on Tuberculosis of the American School Health Association. The Sub-Committee then presented the plan of school certification to the Council of the Missouri State Medical Association and received approval. After this, an informational meeting was held in the county. It was attended by the Missouri tuberculosis con-

NEWTON COUNTY, MISSOURI

OVERALL TUBERCULIN RATES



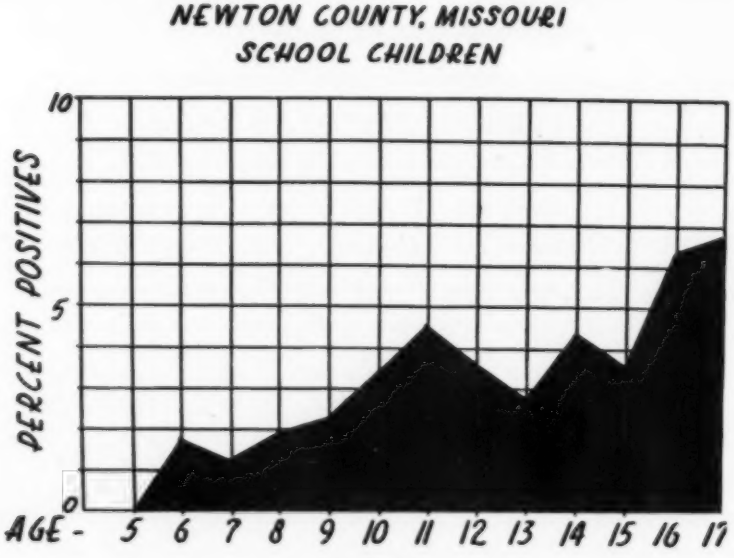
NO. IN GROUP	2215	2578	1271	89	95	110	101	42
NO. POSITIVE	36	93	76	14	24	39	39	15
% POSITIVE	1.6	3.6	6.0	16	25	35	39	36

GRAPH 1

TABLE 1—AGE AND SIZE OF REACTIONS AMONG SCHOOL CHILDREN
Newton County, Missouri

Size	Age			
	5-9	10-14	15-19	Total
Neg. (Inc. 0-4)	2179	2485	1195	5859
5- 9 mm.	18	30	23	71
10-14 mm.	15	23	27	65
15-19 mm.	1	23	15	39
20 mm. and over	2	17	11	30
Total	2215	2578	1271	6064

troller, the district health officer, the county nurses, a health educator, and representatives of each school. The skin testing program was then presented to the regional and local medical and osteopathic societies, which approved the plan. They also agreed to skin test household contacts of school reactors and provide without cost to the individual patient a chest x-ray film for positive reactors found in the schools and among family contacts. This gesture by the physicians was a great contribution to the success of the program. Only the first tuberculin test and the first chest x-ray film of a positive reactor was without charge. Thereafter, the usual fee was paid; or, if the person or family was medically indigent, it was taken care of in the usual manner. The school certification program received endorsement by the Missouri Tuberculosis Association, the Missouri Academy of General Practice, and the Missouri Congress of Parents and Teachers. Following approval of the 42 school boards, a chairman of the county certification board was elected at a citizens' meeting. The chairman then appointed an executive committee with the aid of the Missouri Tuberculosis Association, health authorities, and the Missouri Sub-Committee of the American School Health Association.



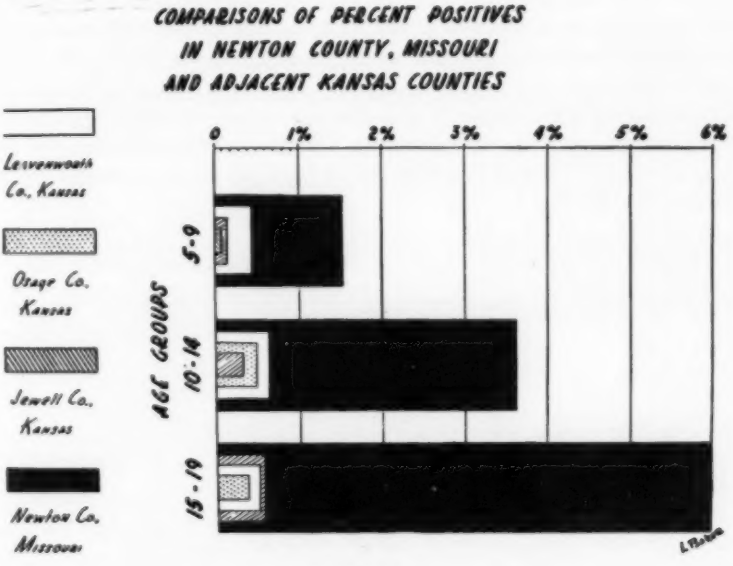
GRAPH 2

Among the members of the executive committee were representatives of the two medical societies, the local health department, the local tuberculosis association, the Parent-Teachers' Association, and civic groups. The executive committee appointed local committees for each school district to handle promotion and education, enlist physicians for volunteer service, handle records and materials, and direct follow-up activities. The very important work of promotion and education was begun approximately eight weeks before the actual testing. A health educator was assigned to the county by the district health office to assist in laying this very important ground work.

The tuberculin employed was purified protein derivative (PPD) furnished by the Division of Health of Missouri to the school screening centers and to physicians for use in their offices to test household contacts of the positive reactors in the schools. The dose was 0.0001 mg., or 5 tuberculin units. The tests were administered intradermally, using platinum needles, which were flamed after each injection, and one drop of solution expelled through the needle to eliminate any coagulum. The tests were read by a physician or a nurse at 48 hours. The erythema and induration were measured in millimeters and recorded. A positive reaction was one in which the induration measured 5 millimeters or more.

Sixteen centers were selected for the testing. Each center was a school located so that the pupils from nearby schools could be transported easily by bus to the testing point.

The testing was done by teams consisting of a physician and a nurse, aided by school personnel and volunteer workers. The number of students to be tested at a center determined the number of teams working there. Each team was able to apply approximately 300 tests per hour if the testing arrangements were well organized.



GRAPH 3

The testing in the 48 schools was completed over a four-week period as scheduled but could have been accomplished in seven to ten days if the schedule had been so arranged. Make-up clinics were arranged so that absentees on the day of the testing were picked up later.

The parents of each school reactor were sent a letter stating the results of the skin test and what follow-up procedures should be carried out. Follow-up of family contacts of positive school reactors was done by public health nurses through home visits during which an explanation of the positive test was given. The family members were then urged to see their family physician for their skin tests, examinations, and chest x-ray films, if indicated.

Certificates were awarded when the skin testing program had been completed in all the schools.

Results

A total of 6,501 persons were tested in the 48 schools in the county. All the schools in Newton County were awarded an "A" or "B" certificate. At least 95 per cent of the students and 100 per cent of the personnel were tested in 31 schools, which qualified for class "A" certificates. (Sixteen schools had 100 per cent of students and personnel tested.) The remaining 17 schools qualified for class "B" certificates by having 80 through 94 per cent of students and 100 per cent of personnel tested.

The over-all tuberculin rates for all persons tested in the survey are shown in Graph 1. There was a gradual increase in the percentage of positive reactors with increase in age, as was expected. There were 1.6 per cent positive in the five through nine age group, with a gradual increase to 6 per cent in the 15- through 19-year age group. Among the school employees, there was a range from 16 per cent positive in the 20 to 29 age group to 39 per cent positive in the 50 to 59 age group. The over-all rate for employees was only 30 per cent.

The rates by age among the school children are shown in Graph 2. No positive reactor was found in the five year-olds; however, the expected rate in this group is small, and only a few of the children tested fell into this age group. The rates increased from 2 per cent at age seven to almost 7 per cent at age 17.

TABLE 2—VARIATIONS IN PERCENTAGE POSITIVES IN SCHOOLS
Newton County, Missouri

Per Cent Positive	No. of Schools
0 - 0.0	15
1 - 1.9	5
2 - 3.9	12
4 - 5.9	9
6 - 7.9	3
8 - 9.9	2
10 - 11.9	0
12 - 13.9	1
14 - 15.9	0
16 - 17.9	1
Total	48

The size of the reaction by age group among children is shown in Table 1. There were 205 reactors among the 6,064 children tested. One hundred thirty-four, (65 per cent) of the reactors, had induration of 10 mm. or more. Studies by the Tuberculosis Division of the United States Public Health Service[1] and the British Medical Society[2] indicate that "breakdown" or reinfection may be more frequent among persons with larger reactions. Studies by Wood *et al.*,[3] indicated a direct relationship between the size of the tuberculin reaction of young children and the likelihood of the presence of active tuberculosis among the adult contacts. As the size of the tuberculin reaction increased, the per cent of active cases found in the contacts increased proportionately. Thus, through a tuberculin testing program we not only find the persons harboring tubercle bacilli, but also may be able to determine the group needing immediate and close follow-up.

The rates for the 48 schools in the county are shown in Table 2. Attention is drawn immediately to those schools with high rates, indicating communities which need immediate control measures. In seven of the schools, 6 per cent or more of the students were positive. Another 21 schools had rates of 2 per cent or more, which is higher than would be expected in a rural county. A tuberculin skin test survey[4] among the rural schools in Boone County, Missouri, in 1958 revealed an over-all rate of 1.8 per cent among school children, while in Newton County the rate was 3.38 per cent among school children. Fifteen schools had no reactor, indicating no tuberculosis problem at this time.

The geographic location of the schools in this county are shown in Figure 1. Most of the schools are in rural areas, and all the schools with 6 per cent or more positives are rural. Rates in the one urban area were among the lowest found, which is in contrast to what was expected.

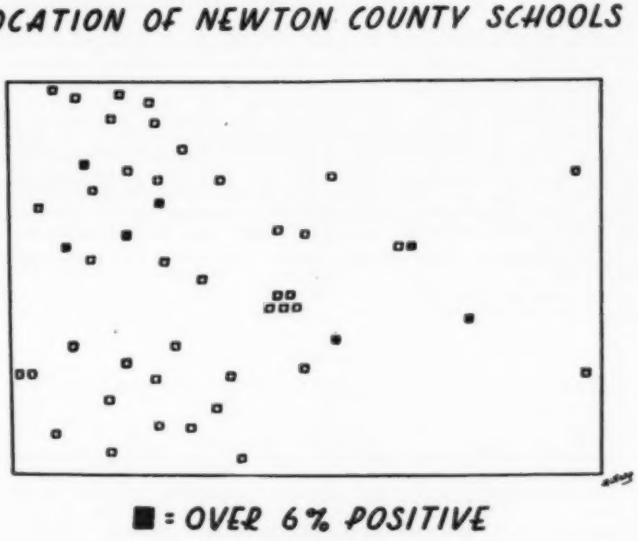


FIGURE 1

Another interesting finding was that the schools with 6 per cent or more positives were grouped in two areas in the county. In each area, the schools were within a five-mile radius of each other.

The rates for different age groups of children in Newton County are compared with rates in adjacent counties in Kansas in Graph 3.[5] The rates in Newton County appear rather high when compared to similar rural counties in Kansas.

Discussion

Tuberculin testing programs in schools can be a valuable and important part of tuberculosis control. The benefits from such a program are many and varied. First of all, the tuberculin rates provide valuable information as to the prevalence of tuberculosis in a community; and a continuing program with repeated testing provides some idea of the incidence of the disease. These findings are important in determining the effectiveness of existing control programs and to find source cases of tuberculosis. In Newton County, 3.38 per cent of the students tested were positive. This figure appears rather high when compared with neighboring rural counties in Kansas (Graph 3). The records show that the death rate from tuberculosis in Newton County in 1958 was much higher than the national average.

In Newton County, it was found that a few schools had extremely high rates and indicated that immediate attention should be given to those communities in which the schools were located. Those schools with the highest rates were discovered to be in two geographic areas of the county.

Case-finding is another important benefit from the skin testing program. One cannot expect a high yield of active cases among the children, although this does occur occasionally. However, the finding of an occasional case in the early stages removes that child from the close contact of many other susceptible children and the early diagnosis offers that child the opportunity of therapy when it is most beneficial. The follow-up of family contacts is most likely to produce the active cases. In the retesting program, the follow-up of converters can be expected to detect new cases among family contacts in the early stages of the disease.

To date, six active cases have been detected by the program in Newton County. Two of these cases were in school children. One was primary tuberculosis, and the other was moderately-advanced disease. Both had positive sputum. Two cases were detected among school personnel and, although one of these persons has refused to come into the hospital for therapy, he has been removed from the school environment. The mother of a school child with positive tuberculin was found to have minimal tuberculosis with positive sputum. One case of active primary tuberculosis was found in a pre-school-age child, the sibling of a student reactor. An additional 15 suspects are being studied at this time. The detection of six active cases in this county is an encouraging yield.

The educational possibilities of a skin testing program may prove to be the most valuable asset. By exposure to repeated testing over the years, the children should learn the value of the test and the implications of positive tuberculin, as well as the value of annual chest x-ray films for positive reactors. Not only the school child, but also the entire family and community become educated in this regard. If the program can establish a routine of yearly examinations with chest x-ray films for the positive reactors, then a great deal will have been accomplished toward detecting the new cases at an early stage when they are most responsive to therapy. Children indoctrinated in this program today will be the leaders in a better program tomorrow.

Another ramification of the program noticed in states where it has been in progress for years is the stimulation of communities to a higher degree of health consciousness.[6] Many families who rarely, if ever, saw a physician have now chosen family physicians and will be more likely to seek medical care for future illnesses.

SUMMARY

The methods and results of the tuberculin skin testing program in Newton County, Missouri, are presented. All 48 schools in the county participated in the program; 6,064 school children and 437 school employees were tested. Among the school children, 205 positive reactors were found, giving a rate of 3.38 per cent. In the adults, 131 of 437 tested were positive, giving a rate of 30 per cent. Six new active cases of tuberculosis were detected, and 15 suspects are being studied. All 48 schools in the county became certified under the school certification program of the American School Health Association, with 31 schools receiving class "A" certificates and 17 schools receiving class "B" certificates. The program in Newton County was felt to be very successful.

RESUMEN

Se presentan los metodos empleados y los resultados obtenidos del plan de pruebas tuberculínicas en el Condado de Newton.

Las 48 escuelas del condado tomaron parte con 6,064 niños escolares y 437 empleados de escuelas, sujetos a las tuberculino-reaccion. Se encontraron 205 reactores positivos entre los niños de escuela, lo que da una proporción de 3.38 por ciento.

Entre los adultos, 131 de 437 probados resultaron positivos dando una proporción de 30 por ciento. Seis casos activos nuevos de tuberculosis se descubrieron y se estudian 15 sospechosos.

Todas las 48 escuelas del condado fueron asi certificadas bajo el plan de certificación de la Asociación Americana de Salud en las escuelas, habiendo recibido certificado de clase "A" 31 escuelas y certificado de clase "B" 17 escuelas. Se cree que el plan del Condado de Newton tuvo much éxito y tiene valor en el control de la tuberculosis.

RESUMÉ

L'auteur présente les méthodes et les résultats d'un programme de contrôle des réactions tuberculiniques dans le Comté de Newton, Missouri. Les 48 écoles du Comté participèrent toutes au programme, ainsi furent testés 6,064 écoliers et 437 personnes appartenant au personnel des écoles. Parmi les écoliers, on trouva 205 d'entre eux avec des réactions positives, soit un taux de 3.38%. Chez les adultes, 131 sur 43 eurent des réactions positives, donnant un taux de 39%. Six nouveaux cas de tuberculose évolutive furent détectés et 15 douteux sont en cours d'observation. Les 48 écoles du Comté eurent un certificat de contrôle de l'Association de Santé Scolaire Américaine, 31 écoles recevant des certificats de classe "A" et 17 écoles recevant des certificats de classe "B." On trouva le programme du Comté de Newton très satisfaisant, et la valeur d'un tel programme pour le contrôle de la tuberculose est mis en discussion par l'auteur.

ZUSAMMENFASSUNG

Die Methoden und Ergebnisse des Tuberkulinkatasters im Kreise Newton (Missouri) werden dargelegt. Alle 48 Schulen des Kreises mit 6,064 Schulkindern und 437 Schulangestellten waren daran beteiligt. Unter den Kindern wurden 205 positive Reaktoren gefunden (3.38%). Bei den Erwachsenen waren 131 von 437 positiv (30%). 6 Fälle von aktiver Tuberkulose wurden aufgedeckt und 15 Verdachtfälle stehen in Überwachung. Alle 48 Schulen des Kreises wurden klassifiziert nach dem Programm der amerikanischen Schulgesundheits organisation, wobei 31 Schulen als Klasse A, 17 als Klasse B eingestuft wurden.

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CARDIAC MASSAGE IN DOGS

In dogs suffering cardiac arrest by ventricular fibrillation, the artificial circulation produced by closed-chest cardiac massage approximated that produced by open-chest cardiac massage; circulation was effectively restored after application of either method; trauma with closed-chest cardiac massage was minimal when only moderate force was applied to the chest; and closed-chest cardiac massage was much less fatiguing to the operator.

Redding, J. S. and Cozine, R. A.: "A Comparison of Open-Chest and Closed-Chest Cardiac Massage in Dogs," *Anesthesiol.*, 22:280, 1961.

Pulmonary Fungus Infections Associated with Steroid and Antibiotic Therapy*

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Aspergillus, Mucor and Candida are common fungi which are present in abundance in most environments. Although they are usually considered saprophytic, cases of human infection have been reported with increasing frequency in recent years.[1,3,5,6,11,14-17] During the past three years twenty cases of secondary pulmonary infection due to one or more of these fungi have been observed at autopsy at Charity Hospital of Louisiana in New Orleans, whereas only four cases were encountered in the preceding five year period. Though the cause of the increase is not definitely established, it is generally believed that the extensive administration of cortisone and related steroids, ACTH and antibiotics to chronically ill patients may be an important factor.[1,3,5,6,11,14-17] Blood dyscrasias and malignant diseases as well as diabetes mellitus were the primary or associated illnesses in the majority of our cases as well as in those reported by other groups.[1,5,6,14,16,17] In most instances the fungus infection, although classified as secondary, had produced extensive destructive lesions in the lung sufficient to serve as a direct or contributory cause of death.

Observations

A. *Clinical Data*

The clinical data in the twenty cases of pulmonary fungus infections are summarized in Table 1. These cases were encountered over a three year period from April, 1955 to April, 1958. The age of the patients ranged from two months to 73 years, with 12 being older than 50 years. Ten were men and 10 were women.

Pulmonary aspergillosis was present in seven cases, mucormycosis in six, and candidiasis in eight. Case 2 had a combined infection with Aspergillus and Candida. Cultures for fungi were obtained at necropsy in seven of the 20 cases.

Blood disorders and malignant neoplasms were the most common primary disorders and accounted for nine of the cases. Of the six with blood diseases, three had lymphocytic leukemia, one had agranulocytosis, one had a myeloproliferative disorder with pancytopenia, and one had afibrinogenemia. The three with other malignancies had carcinomas of the cervix, esophagus, and rectum, respectively. An additional case of "lethal midline granuloma" might also be classed as a malignancy.

Diabetes mellitus was present in six, but was the primary disorder in only one (Case 6). Diabetes was associated with other serious condi-

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tions in the remaining five patients. There were three patients with liver disease, eight with cardiovascular-renal disease, and two with systemic lupus erythematosus. All had suffered from one or more severe chronic diseases for periods ranging from several weeks to several years.

Aspergillus infections were present in four of the six patients having blood dyscrasias, with one also having combined infection with Candida. The other two were infected with Candida and Mucor respectively. Of the four with other neoplastic diseases, including the one with the "lethal midline granuloma," two had pulmonary aspergillosis and one each had infections with Mucor and Candida. In those with diabetes there were three with mucormycosis and three with candidiasis.

Fifteen of the 20 had been treated with both steroids and antibiotics, four had received antibiotics alone and only one had received neither type of agent. The latter patient was unusual in that he had a carcinoma of the esophagus which had ruptured into the right lung.

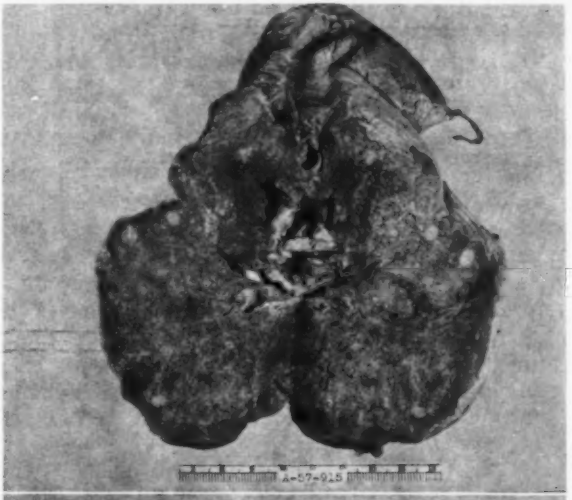

Figure 1

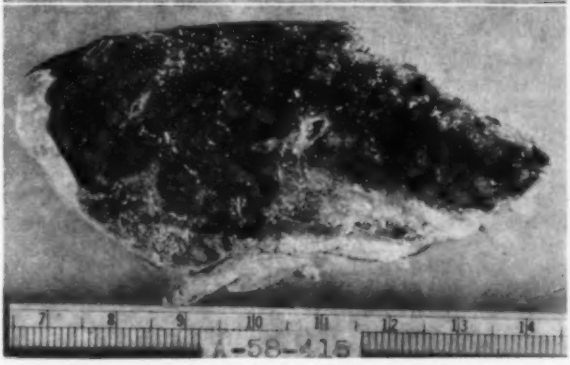

Figure 2

FIGURE 1 Lung (Case 4): Mucormycosis; multiple, nodular lesions throughout lung. In this instance the hemorrhage that often surrounds the nodules is not present. FIGURE 2 Lung (Case 2): Aspergillosis and candidiasis: Hemorrhagic areas of bronchopneumonia together with nodular lesions.

The duration of therapy with steroids and antibiotics was variable. In eight, steroid therapy was given for less than two weeks. Five had received steroids for a period of one to three months, one had been treated for more than three years, and one had taken steroids for an unknown period of time.

Antibiotic therapy was given to eight for a period of less than two weeks, to 10 for a period of two to four weeks, and to one for two months. All of these patients received both penicillin and broad-spectrum antibiotics.

In addition to pulmonary fungus infections, other organs were involved in at least 11 of the 20 patients. Widespread systemic involvement was present in four with candidiasis (Cases 7 and 8). Two patients with pulmonary aspergillosis had Candida infections in other organs, the esophagus in one case and the oral mucosa, bladder, and vagina in Case 2. In two patients with pulmonary mucormycosis, Candida infections were present in the duodenum and oral mucosa. In the seven with pulmonary aspergillosis the infection was confined to the lungs in all but one. Of the six with mucormycosis, extrapulmonary involvement was present in only one. The clinical findings suggested that cerebral mucormycosis may have been present in Case 6, but the brain was not examined. Severe bacterial pneumonias were also a complicating factor in seven of the patients in addition to the pulmonary fungus infections.

A review of the clinical histories reveals that in ten of the patients there were changes in the clinical course which could reasonably be attributed to the development of the secondary fungal infection. These included symptoms, physical signs, and x-ray evidence of pneumonia which first appeared after prolonged steroid and antibiotic therapy and failed to respond to antibiotic therapy. In addition, oral, vaginal, and cutaneous candidiasis developed in some patients while they were on steroid therapy. Yeast forms were seen on urinalysis and were cultured in some cases.

B. *Gross Pathology*

At necropsy a gross diagnosis of bronchopneumonia was made in many instances but fungus infection of the lungs was rarely suspected. On subsequent review of the material in the whole series it was found that the gross lesions most often associated with the fungus infections were firm, grey, 0.5-3 cm. nodules scattered irregularly throughout the lungs (Figure 1). In most cases of pulmonary aspergillosis and mucormycosis, but not in candidiasis, the nodular consolidations in the lungs were surrounded by a zone of hemorrhage (Figure 2). Other non-specific changes were areas of infarction and abscess formation.

C. *Microscopic Pathology*

Our 20 cases could be diagnosed by histologic examination of tissue sections. Our criteria for the histologic identification of these fungi in tissue sections were based in part on careful microscopic comparison with the seven cases in which cultural confirmation was available as well as on the differentiating features described by others.[1,2,14,16,17] Careful attention to histologic detail is necessary in attempting to differentiate

Aspergillus, Mucor, and Candida since all three usually develop filamentous forms within the tissue. The histologic features characteristic of each organism will be described separately.

1. Aspergillus.

The hyphae were uniform, septate, and 3 to 4 microns in diameter with frequent tree-like branching. Long segments of septate hyphae were usually seen in roughly parallel arrangement with branching at acute angles (Figure 3). In other instances a radial arrangement was apparent, particularly where the infection involved bronchi, bronchioles, and blood vessels (Figure 4). Chlamydospores were occasionally present. In only one case were conidiophores with sterigmata and conidiospores identified and these were found within the lumen of the bronchus (Figure 5). Hyphae often appeared to have originated within bronchi and extended through bronchial walls into the surrounding lung parenchyma (Figure 5). A hemorrhagic bronchopneumonia was usually present in these areas. Adjacent areas of necrosis with polymorphonuclear cell response were frequently observed. Mycelial thrombi with a radial arrangement of hyphae were common within blood vessel lumens. In one case a few chronic granulomas that contained no identifiable fungi were found. In two cases hyphae extended into and through the visceral pleura of the lungs. In general the pattern of growth of the hyphae in tissues showed an almost complete disregard for natural tissue planes or pre-existing anatomic structures. The hyphae stained well with the Gridley stain and to lesser extent with periodic acid Schiff and hematoxylin and eosin stains.

2. Mucor

The hyphae were predominantly non-septate and showed marked variation in thickness, ranging from 5 to 20 microns. The branching was irregular with frequent right angle branches. As a rule, only short segments of hyphae were seen in tissue, suggesting that the hyphae were characteristically bent and angulated so as to run for only short distances in any single plane (Figure 6). Frequently, they appeared as irregular twisted ribbon-like forms. In only one case were sporangia identified and these were found in an area of compact mycelial growth. Hyphae were often seen invading the walls of bronchi and bronchioles and extending into bronchiolar and alveolar lumens. Many polymorphonuclear cells were present in these areas. In most cases there was extensive invasion of pulmonary blood vessels with resulting thrombosis. This is one of the striking characteristics of infections with this fungus. Occasionally, areas of infarction were present in which hyphae were found. The hyphae stained well with hematoxylin and eosin and poorly with periodic acid Schiff and Gridley stains.

3. Candida

In tissue sections Candida were present as either yeast or filamentous forms or combinations of the two. Budding yeast cells were frequently observed. The filamentous forms were uniform, often club-shaped and septate with little branching, and measured about 2 microns in diameter. Candida in both the filamentous and yeast forms were found chiefly

TABLE 1—PRIMARY AND ASSOCIATED DISEASES, THERAPY, AND SPECIES OF FUNGUS IN 20 CASES OF SECONDARY PULMONARY FUNGUS INFECTION

Cases	Patient	Age	Color*	Sex*	Primary and Associated Diseases	Steroid Therapy Agents	Steroid Therapy Duration	Antibiotic Therapy** Agents	Antibiotic Therapy** Duration	Pulmonary Fungus
1	L.F.	50	W	M	Myeloproliferative disorder Pancytopenia Congestive heart failure	ACTH Cortisone	92 days	Penicillin Streptomycin Tetracycline	63 days	*Aspergillus flavus*†
2	A.J.	27	C	F	Systemic lupus erythematosus	Cortisone Hydrocortisone	94 days	Penicillin Streptomycin Tetracycline Erythromycin	24 days	*Aspergillus flavus*†
3	E.W.	60	C	F	Lymphocytic leukemia	Prednisone	9 days	Penicillin Chloramphenicol	15 days	*Aspergillus flavus*†
4	F.T.	29	W	F	Agranulocytosis Septicemia	Hydrocortisone	7 days	Penicillin Tetracycline Chloramphenicol Streptomycin Erythromycin Ristocetin	10 days	*Aspergillus flavus*† *Candida albicans*†
5	O.C.	46	W	F	Carcinoma of cervix Pyelonephritis Acute renal failure	Adrenal cortical extract Cortisone	10 days	Penicillin Streptomycin Erythromycin	23 days	Aspergillus
6	F.A.	2 mo.	C	M	Hepatitis Afibrinogenemia	Hydrocortisone	6 days	Penicillin Chloramphenicol Tetracycline	17 days	Aspergillus
7	I.C.	68	C	M	Carcinoma of esophagus	none		none		Aspergillus
8	J.B.	41	W	F	Nephrotic syndrome	Prednisone ACTH	79 days	Penicillin Tetracycline	21 days	*Rhizopus rhizopodiformis*†
9	B.M.	57	W	F	Laennec's cirrhosis Hepatic coma	Hydrocortisone Cortisone	8 days	Penicillin Tetracycline Chloramphenicol	6 days	Mucor
10	A.H.	73	C	M	Carcinoma of Rectum Arteriosclerotic heart disease Uremia	none		Tetracycline Penicillin Streptomycin	12 days	Mucor

TABLE 1—Continued

11	R.J.	63	C	M	Lymphocytic leukemia Diabetes mellitus	none		Penicillin Streptomycin Erythromycin	13 days	Mucor
12	F.N.	55	W	F	Hypertensive cardio-vascular disease Diabetes mellitus	ACTH	10 days	Penicillin Tetracycline Chloramphenicol	18 days	Mucor
13	F.W.	58	W	F	Diabetes mellitus	Hydrocorti-sone	1 day	Penicillin Chloramphenicol	12 days	Mucor
14	M.N.	66	W	M	Lethal midline granuloma	Cortisone	Not known	Penicillin Tetracycline Streptomycin Mycostatin	29 days	*Candida albicans*†
15	Y.S.	16	W	F	Systemic lupus erythematosus Diabetes mellitus	Prednisone ACTH Hydrocortisone	3 yrs	Penicillin Tetracycline Chloramphenicol	21 days	*Candida albicans*†
16	A.T.	54	C	F	Rectal stricture Lymphopathia venereum Intestinal obstruction Diabetes mellitus	none		Penicillin Tetracycline Streptomycin	22 days	Candida
17	W.P.	64	C	M	Diffuse pulmonary fibrosis Cor pulmonale Myocardial infarction	none		Penicillin Streptomycin	1 day	Candida
18	L.R.	18	C	M	Lymphocytic leukemia	Prednisone Hydrocortisone	63 days	Penicillin Streptomycin	2 days	Candida
19	J.T.	73	W	M	Laennec's cirrhosis Pyelonephritis	Hydrocorti-sone ACTH	11 days	Penicillin Chloramphenicol Streptomycin	26 days	Candida
20	S.L.	28	C	M	Idiopathic pericarditis Diabetes mellitus Acute renal failure	Prednisone	92 days	Penicillin Streptomycin INH, PAS } 3 months	8 days	Candida

*W=white C=negro M=male F=female

**Antibiotics were given throughout the stated period but in many instances not all the agents listed were given simultaneously.

†Indicates identification of fungus by culture.

within bronchi, bronchioles, and alveolar spaces but were also seen in areas of necrosis (Figure 7). Blood vessel involvement was observed only occasionally. Candida stained well with gram, periodic acid Schiff and Gridley stains, but less satisfactorily with hematoxylin and eosin.

The clinical data in twenty cases of pulmonary fungus infections are summarized in Table 1. Nine cases are reported here in more detail.

Case Reports

Case 1 (A. J. T-47-272251, A-55-1514): This 27 year-old Negro female was admitted on September 30, 1955. A diagnosis of rheumatic fever had been made in January, 1955, and she had been treated with cortisone for an undetermined period of time. She had been hospitalized in August with a recurrence of symptoms at which time a diagnosis of systemic lupus erythematosis was established. She was treated with cortisone, starting at 400 mg. daily, and tapered to 100 mg. daily. She received penicillin and streptomycin for 8 days because she was febrile and the cortisone was gradually reduced to 25 mg. by the time of discharge. One week later she was readmitted with a generalized erythematous and vesicular rash, severe anemia, and azotemia, and was treated with hydrocortisone, erythromycin and tetracycline for nine days until her death.

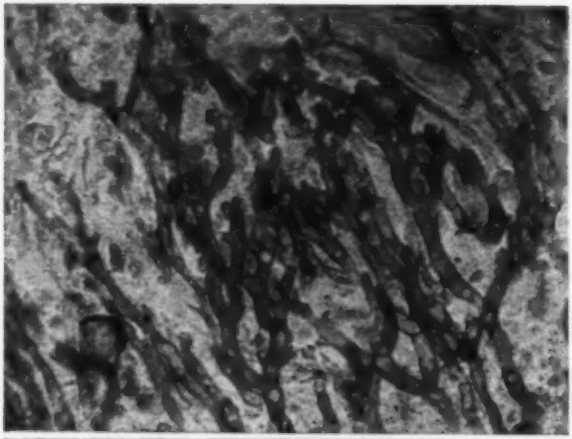

Figure 3

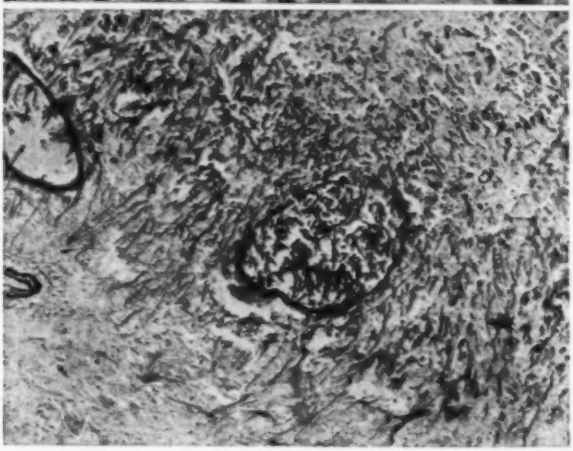

Figure 4

FIGURE 3: Lung (Case 3): Aspergillosis; typical septate hyphae with tree-like branching; Gridley stain, x 570. FIGURE 4: Lung (Case 3): Aspergillosis; hyphae within a small blood vessel and adjacent area; Gridley stain, x 135.

The necropsy findings were pulmonary aspergillosis and systemic lupus erythematosus with involvement of the heart, spleen, kidney, brain and skin. The lungs were moist and showed scattered irregular regions of hemorrhage, 0.8-2 cm. in diameter. The bronchial mucosa was hemorrhagic. Cultures of the lung grew out *Aspergillus flavus*. Microscopically, a section of a bronchus showed necrotizing changes of the walls along with extensive hyphal infiltration. Hyphae, conidiophores with conidiospores of Aspergillus and neutrophils were present in the lumen (Figure 5). Hyphae were seen invading the surrounding parenchyma and also the blood vessels. Other areas showed a hemorrhagic bronchopneumonia with numerous hyphae. A section of the larynx showed ulceration with hyphal growth.

Case 2 (F. T. T-58-286403, A-58-415): This 29-year-old white female was admitted on March 4, 1958, 7 weeks after delivery of a premature infant. Three weeks prior to admission she developed symptoms of influenza, as well as a foul-smelling brown vaginal discharge, dysuria, backache, and crusted lesions on the lips, face, and right hand. She received tetracycline for 5 days without improvement. She appeared acutely ill and her temperature was 105.6°F. The oral mucosa was beefy red with white plaques present on the hard palate and tonsils. Infected pustular lesions were present on the right hand with lymphangitis and regional lymphadenopathy. She had lower abdominal tenderness and a serosanguinous vaginal discharge with white patches present on the vaginal mucosa and cervix. A severe anemia was present and the WBC count was only 250 per cu. mm. The bone marrow was compatible with agranulocytosis. Several blood cultures and bone marrow cultures were negative. *Staphylococcus aureus* was cultured from the throat and vagina and *Candida albicans* from the mouth lesions. A chest x-ray was normal.

She was treated with large doses of penicillin, chloramphenicol, streptomycin, erythromycin, and later ristocetin. Hydrocortisone was given for 7 days in doses ranging from 300-600 mg. per day. During this time her mouth became overgrown with Candida and râles were heard at the right lung base. WBC counts ranged from 200-800 per cu. mm. She became jaundiced and on the 8th hospital day, blood cultures grew out *Aerobacter aerogenes* and gram positive cocci. She died with severe respiratory symptoms the following day.

The necropsy findings were agranulocytosis, septicemia with *Staphylococcus aureus* and *Aerobacter aerogenes*, multiple ulcerations of stomach and duodenum, Candida esophagitis, Candida cystitis and vaginitis, bronchopneumonia, and pulmonary aspergillosis and candidiasis. The lungs revealed a fibrinous pluritis, congestion, edema, and scattered areas of consolidation (Figure 2). Bacterial cultures grew out *Aerobacter aerogenes* and fungus cultures grew out *Aspergillus fumigatus* and *Candida albicans*. Microscopically, there were many foci of yeast-like fungi of Candida present within alveoli and blood vessels. In addition, there were foci of septate hyphae of Aspergillus within bronchioles and alveolar spaces. Few inflammatory cells were present.

Case 3 (F. A. T-57-262576, A-57-1481): This two months-old male Negro child was admitted because of jaundice. One week prior to admission he was treated for pharyngitis and bilateral otitis media with penicillin and tetracycline for five days. However, he became jaundiced, hyperirritable, and developed muscle rigidity, hepatosplenomegaly, and rigidity of the neck. A severe anemia was present. The urine was positive for bile and negative for urobilinogen. The serum bilirubin was 7.68 mg. per cent, mostly the direct type. The cephalin flocculation and thymol turbidity tests were normal. The cerebrospinal fluid was free of cells, but the protein was 130 mg. per cent. The stools were very pale. Blood and spinal fluid cultures were negative. He was treated with penicillin and later chloramphenicol and tetracycline for 12 days. A hemorrhagic tendency developed and a hematological study disclosed afibrinogenemia which responded to blood transfusions and fibrinogen. A daily dose of 100 mg. of hydrocortisone was given for 6 days, without improvement. The serum bilirubin rose to 23.7 mg. per cent. The temperature ranged from 99°-102°F. and 10 days after admission he developed signs of pneumonia and an x-ray showed densities in the right lower and middle lobes. He died 2 days later.

The necropsy disclosed hepatitis, jaundice, hemorrhagic diathesis with subarachnoid hemorrhage and hemorrhage into the lungs, kidneys and gastro-intestinal tract, and bilateral bronchopneumonia with pulmonary aspergillosis. The lungs were moist and hemorrhagic. There were scattered multiple, small gray nodules, surrounded by hemorrhage, as well as small thrombi. Microscopically, there were numerous foci of necrosis in which hyphae of Aspergillus were present in a radial arrangement. These areas involved bronchi, alveoli, and blood vessels, and were frequently surrounded by hemorrhage. Numerous thrombi containing hyphae were present (Figures 3 and 4). In addition, there were areas of bronchopneumonia with hyphae present.

Case 4 (J. B. T-56-227265, A-57-915): This 41-year-old white female was first admitted on July 30, 1956, with a six week history of severe generalized edema. A nephrotic syndrome due to chronic glomerulonephritis was diagnosed. She was placed on bed rest and a low salt diet and had a slight diuresis before her discharge four weeks later. Her final admission was in February, 1957. She received several courses of prednisone during the next 3 months, with the dose ranging from 40-60 mg. per day, with several injections ACTH. She had a moderate diuresis but her general condition

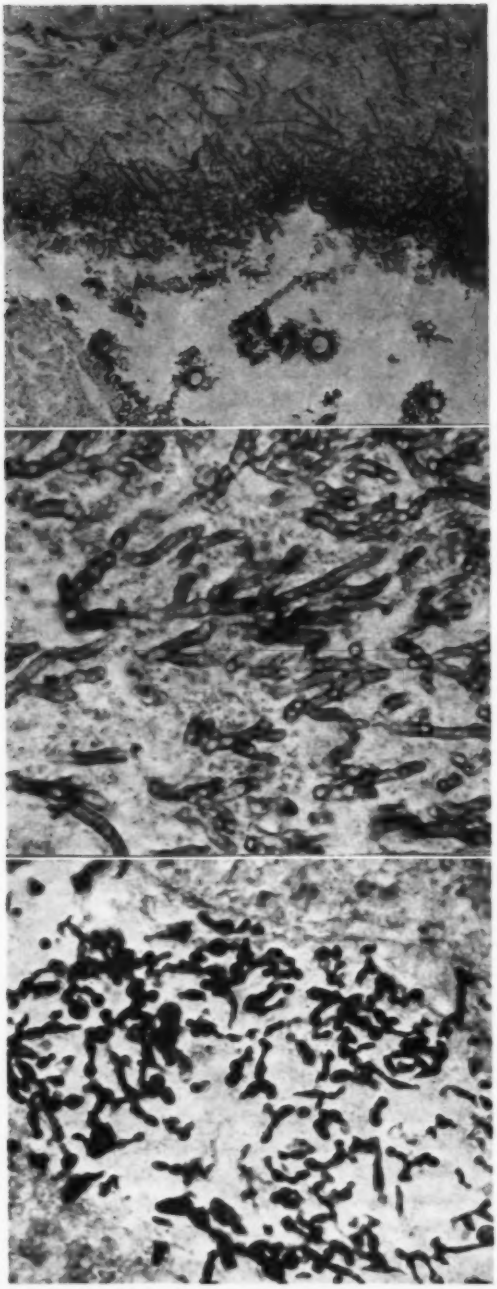

Figure 5

Figure 6

Figure 7

FIGURE 5 Lung (Case 1): Aspergillosis; hyphae in wall of bronchus, with sterigmata in bronchial lumen; Gridley stain, x 110. FIGURE 6 Lung (Case 4): Mucormycosis: non-septate, branching hyphae; hematoxylin and eosin stain, x 475. FIGURE 7 Lung (Case 8): Candidiasis; filamentous and yeast forms of Candida in a blood vessel; PAS stain, x 750.

gradually deteriorated with increasing azotemia. A low grade fever developed and penicillin and tetracycline were given for 14 days when she developed signs and symptoms of pneumonia. Her condition became worse and she developed a generalized erythematous pustular rash, cellulitis of the right calf, and a vulvitis believed to be due to Candida. She died in coma 4 months after admission.

The necropsy findings were membranous glomerulonephritis, staphylococcal septicemia with abscesses in the lungs, myocardium, kidneys and skin, chronic pancreatitis, duodenal ulcerations with Candida and erosion into the pancreas, extensive suppurative bilateral bronchopneumonia, and pulmonary mucormycosis. There were multiple, 1-2 cm. yellowish nodular lesions throughout both lungs (Figure 1). Microscopically, there was an extensive necrotizing bronchopneumonia with numerous colonies of bacteria. In some of these areas non-septate hyphae were present in a radial arrangement (Figure 6). A section of the duodenal ulcer and pancreas showed Candida involvement of the ulcer with extension into a large artery. Cultures of the lung grew out *Rhizopus pygaeus Naumov (Rhizopus rhizopodiformis)*.

Case 5 (B. M. T-47-207607, A-56-122): This 57-year-old white female was admitted on January 16, 1956, with cirrhosis of the liver secondary to chronic alcoholism. Jaundice, hepatomegaly, ascites, and signs of hepatic coma were present. She was febrile and anemic. She was treated with hydrocortisone for 8 days and also penicillin, tetracycline, and chloromycetin. Transfusions were given when her hematocrit became low. However, azotemia developed and she died in shock following severe hematesis.

The necropsy findings were Laennec's cirrhosis with marked fatty changes, jaundice, esophageal varices with hemorrhage, chronic pancreatitis, bilateral bronchopneumonia and pulmonary mucormycosis. The lungs showed small, depressed, red areas with pus in the central portions. Microscopic examination showed many areas of extensive bronchopneumonia. There were broad non-septate hyphae of mucor present within bronchioles, extending into the surrounding parenchyma and through the pleura. Numerous mycelial thrombi were seen in these areas.

Case 6 (E. W. T-47-272948, A-58-304): This 58-year-old white female diabetic was admitted in coma. She had diabetic retinopathy, renal disease, hypertension, and cardiac disease. Her respiration was labored and examination revealed peripheral edema, generalized hyperreflexia, and opisthotonos. A moderate anemia and leukocytosis was present. The urine showed 4 plus protein and was negative fqr sugar and acetone. A lumbar puncture revealed normal cerebrospinal fluid. A blood sugar was 85 mg. per cent and BUN, 40 mg. per cent. She was given intravenous fluids with insulin coverage and large doses of penicillin and chloramphenicol. Her urine output was low with marked proteinuria and pyuria present. Her temperature ranged from 99°-102°F. She remained edematous and developed progressive azotemia. A single dose of 300 mg. hydrocortisone was given on the 14th hospital day. Her condition became worse and she died on the 17th hospital day.

The necropsy findings were diabetic glomerulosclerosis, interstitial pancreatitis, arteriosclerotic heart disease, pulmonary edema, bronchial adenoma, and pulmonary mucormycosis. Microscopically, a section of a bronchus showed extensive necrotizing changes. There was a large collection of hyphae containing numerous sporangia of Mucor. The hyphae showed marked variation in size and shape with frequent sharp branching. Adjacent to the described bronchus, there was a large thrombosed artery which contained numerous hyphae. Other areas showed pulmonary edema and hyphae. Permission for examination of the brain had not been granted.

Case 7 (M. N. T-57-275665, A-57-2040): This 66-year-old white male was admitted on November 12, 1957, with a 3 year history of painful ulcerating lesions of the palate and nasopharynx with a foul-smelling oral and nasal discharge, chronic sore throat, and weight loss. He also had a 25-year history of chronic sinusitis. In 1954 the nasopharyngeal lesion was biopsied several times and reported as a nonspecific granuloma. He was treated with antibiotics without any specific improvement, and was given a short course of cortisone therapy with some improvement. He continued to take the cortisone on his own for an undetermined period of time. When he was seen again, he was malnourished. The lesions were still present. A chest x-ray showed infiltrations in the right lower lobe, scattered calcifications and fibrotic changes, and was suggestive of bronchiectasis in the right lower lobe. Studies for acid fast bacilli were negative. Three biopsies of the oral lesions revealed only a granulomatous ulcerating lesion with extensive necrosis, chronic inflammation, and masses of Candida and bacteria. *Candida albicans* was cultured and yeast cells were seen on direct scrapings. Bone x-rays were negative for metastatic lesions and sinus x-rays showed sinusitis. He was treated with penicillin and tetracycline but a low grade fever persisted. Mycostatin was given during the last week of life. He died one month after admission.

Necropsy revealed an ulcerating granulomatous lesion involving the soft and hard palate, nasopharynx, larynx, epiglottis, which was compatible with the lesions of granuloma gangraenescens, or the so-called lethal midline granuloma. One kidney and the spleen were also involved by lesions. Most of the lesions were necrotic and there was a superimposed Candida infection. A severe bronchopneumonia with abscess

formation and pulmonary candidiasis was present. Multiple small abscesses were present in both lower lobes. Microscopically, there was a confluent bronchopneumonia with abscess formation with thin filamentous forms and a few yeast-like forms present. In one area fungi were present in a thrombosed artery with extension into the wall of the artery. Cultures of the lung and oral lesions grew out *Candida albicans*.

Case 8 (Y. S. T-58-288818, A-58-714): This 16-year-old white female was admitted on April 2, 1958. A diagnosis of systemic lupus erythematosus had been made 3 years previous and she was treated with cortisone during that time. In February, 1958, she was hospitalized elsewhere for 1 month because of exacerbation of her symptoms and a renal infection. She was continued on steroids but shortly after discharge she developed knee pains, fever, malaise, and a cough and was hospitalized at Charity Hospital. She was febrile and had a lupus skin rash as well as bilateral costovertebral angle tenderness and 1 plus pretibial edema. She had a slight anemia, proteinuria, and pyuria. Urine cultures grew out *Escherichia coli* and *Proteus mirabilis*. Chest x-ray and ECG were normal. She was treated with large doses of prednisone, starting at 240 mg. per day, which was gradually reduced to 70 mg. per day by the 3rd week. She also received ACTH gel simultaneously ranging from 40-60 units per day. Tetracycline was given for 1 week. She became afebrile after several days and improved symptomatically. On April 19, she had 2 plus glycosuria and during the following week developed severe diabetic acidosis. A urine culture grew out yeast forms. She was taken off oral prednisone, but was given hydrocortisone, 600 mg. per day intravenously during the final 2 weeks. The acidosis was reversed but she developed acute pulmonary edema and required digitalization. Her blood pressure fell to low levels and arterenol (Levophed) was required for several days. During the final 2 weeks she was on large doses of penicillin, tetracycline, and chloramphenicol. Her condition was complicated by problems with fluids and electrolytes, pyelonephritis, oliguria, high fever, and several bouts of hematemesis. During the last 2 days she had several convulsions and died in acute pulmonary edema.

The necropsy findings were systemic lupus erythematosus, severe acute pyelonephritis due to *Candida albicans*, multiple gastric ulcerations with Candida, Candida abscesses in the heart, skeletal muscle, and thyroid gland, acute pulmonary edema and congestion, and bronchopneumonia. Cultures of the lung grew out *Candida albicans*. Nodular areas, with gray centers were present in the lower lobes of both lungs. Microscopically, large collections of small filamentous forms, many of which showed distinct budding typical of Candida were present in the bronchi, bronchioles, and blood vessels, as well as within the alveoli (Figure 7).

Case 9 (L. R. L-56-231440, A-57-654): This 18 year-old Negro male was admitted in November, 1956, with a 2 month history of arthralgias, fever, headaches, weakness, weight loss, and generalized lymphadenopathy. He had an anemia and the white blood cell count was 2940, with 51 per cent lymphocytes. A bone marrow aspiration revealed many clumps of lymphoblasts and a diagnosis of aleukemic leukemia was made. In addition, a hemolytic anemia was suspected. He was placed on 6-mercaptopurine (6-MP) and prednisone, 60 mg. per day. The prednisone was gradually reduced in dosage and discontinued after 3 weeks. The 6-MP was discontinued when the WBC count decreased. It was later resumed along with prednisone when the anemia recurred with the latter given at a dose of 20-30 mg. per day for 33 days. He was readmitted in April, 1957, because of headaches and vomiting of 1 week duration. He appeared lethargic and was tender over the left temporal area. Two days after admission he had a grand mal convulsion and because of the possibility of leukemic infiltration of the brain, received x-ray therapy to the skull. In addition he received prednisone for 5 days and then hydrocortisone for 5 days. However, the convulsions continued, the blood pressure became elevated and his sensorium became more clouded. H developed a left upper extremity paresis. His temperature ranged from 99.2° to 102°F. Several blood cultures were negative. Lumbar punctures revealed clear fluid under elevated pressure. Penicillin and tetracycline were given for 2 days before he died.

The necropsy diagnoses were lymphatic leukemia, bilateral bronchopneumonia, and pulmonary candidiasis. Microscopically, there were areas of bronchopneumonia and yeast forms of Candida were present within bronchioles and alveolar spaces with minimal surrounding inflammatory reaction. No filamentous forms were seen.

Discussion

Most patients who develop secondary pulmonary fungus infections are already seriously ill with some other disease and the complicating fungus infection is seldom suspected clinically. Unfortunately there are no specific signs, symptoms, or x-ray findings that are definitely diagnostic. However, cultures of sputum, blood, urine and any accessible lesions may be helpful. The hazard of developing fungus infections of the lungs should be kept in mind in patients on prolonged steroid and antibiotic therapy, especially if a pneumonia develops that does not respond to treatment. In such patients, the presence of oral, cutaneous, or vaginal candidiasis should suggest the posisbility that the infection may also involve the lungs. "Saprophytic" fungi when found in cultures taken from chronically ill or dibilitated patients often represent something more than harmless contaminants.

Chronically ill persons have a diminished resistance against many types of infection and commonly die as a direct result of secondary bacterial pneumonia. In our own series, seven had severe bacterial bronchopneumonia in addition to the fungus infection. Diminished host resistance has been emphasized as an important factor in both bacterial and fungus infections, especially in patients with lymphoma, leukemia and other blood disorders.[14,17] Treatment with ACTH and corticoid hormones is known to reduce host resistance to many bacterial infections[8] and for this reason antibiotics are often administered in conjunction with these steroids. However, there is evidence to suggest that both antibiotics and cortisone decrease host resistance to fungus infections.[4,7,10-12,14,17] The fact that nineteen of our twenty patients with pulmonary fungus infections had been treated with steroids, antibiotics or both suggests that this therapy may have played a significant role in rendering them susceptible to infection with fungi that are ordinarily non-pathogenic for man.

Further support for this conclusion is derived from experimental studies. Using cultures of *Aspergillus flavus* obtained from Case 1, it was found that untreated normal mice could inhale large numbers of spores with relative impunity but that mice treated with cortisone and antibiotics were highly susceptible to fatal pulmonary aspergillosis on inhaling a like quantity of spores.[12] It has similarly been shown that cortisone is capable of lowering resistance to infection with various "saprophytic" fungi.[7,10] In addition to their effect on host resistance there is experimental evidence that antibiotics as well as corticoids may directly enhance the growth of certain fungi.[4,10]

The mechanisms by which antibiotics and steroids influence the development of fungus infections are not well understood, but alteration of bacterial flora,[11,15] direct enhancement of fungus growth,[4,7,10,12] inhibition of the inflammatory reaction and alteration in immunologic responses[8,13] are possible factors.

The evidence suggesting that steroids and antibiotics may have played a role in the recent increase of secondary fungus infections of the lungs adds another item to the list of dangers attending to indiscriminate use of these agents. Though such complications are admittedly uncommon, a more circumspect use of steroids and antibiotics might further decrease their frequency. It is equally important to attempt to diagnose such infections as do occur while the patient is alive, since new antifungal drugs such as amphotericin B are becoming available and may be effective.[9]

Culture is essential for the definitive identification of these fungi. Cultural confirmation has seldom been available in reported cases of secondary fungus infections of the lung, but fortunately, careful histopathologic study of infected tissues can provide a fairly reliable presumptive identification. In one of the seven cases confirmed by culture in our series, *Rhizopus pygmaeus Naumov (Rhizopus rhizopodiformis)* was recovered from the lungs. Human infection with this particular species has not been previously reported.

SUMMARY

Twenty cases of pulmonary fungus infection due to Aspergillus, Mucor, and Candida were observed at necropsy during the past three years at Charity Hospital at New Orleans. Nineteen of them were associated with steroid and/or antibiotic therapy. The incidence of pulmonary fungus infection due to so-called "saprophytic" fungi has increased in recent years and appears to be related to the use of steroids and antibiotics in chronically ill patients. Awareness of the hazard of such infections is necessary in prevention or in diagnosis and treatment.

ACKNOWLEDGEMENT: We are greatly indebted to Dr. Lorraine Freidman and Dr. John D. Schneidau, Jr., of the Department of Microbiology, Tulane University School of Medicine, for fungus cultures and species identification.

RESUMEN

Durante los pasados tres años se observaron en Charity Hospital de Nueva Orleans veinte casos de infecciones pulmonares debidas a aspergilus, mucor y cándida, en las autopsias.

Diecinueve de ellas estaban asociadas a tratamiento con esteroides y con antibióticos. La incidencia de la infección de hongos pulmonares debida a los hongos llamados "saprofitos" ha aumentado en los últimos años y parece estar en relación con el uso de esteroides y antibióticos en los enfermos crónicos. Es necesario estar alerta ante la ocurrencia de tales infecciones para su prevención, diagnóstico y tratamiento.

RESUMÉ

20 cas d'infection pulmonaire fongique due à *aspergillus, mucor* et *candida,* furent observés à l'autopsie pendant les trois dernières années à l'Hopital de la Charité à New Orleans. 19 d'entre eux avaient subi une thérapeutique stéroïde ou antibiotique. La fréquence de l'infection pulmonaire fongique due à de prétendus "saprophytes" a augmenté dans les récentes années, et semblent en relation avec l'emploi des stéroïdes et des antibiotiques chez les malades chroniques. La connaissance du danger de telles infections est nécessaire à la prévention, au diagnostic et au traitement.

ZUSAMMENFASSUNG

Es wurden 20 Fälle von pulmonaler Pilzinfektion durch aspergillus, mucor und candida beobachtet bei den Sektionen während der letzten Jahre im Charity-Hospital von New-Orleans. 19 von Ihnen hatten Beziehung zu einer Steroid- und/oder antibiotischen Therapie. Die Häufigkeit einer pulmonalen Pilzinfektion mit sogenannten "saprophytischen" Pilzen hat in den letzten Jahren zugenommen und dürfte in Beziehung stehen zu dem Gebrauch von Steroiden und Antibiotizis bei chronisch kranken Patienten. Man muß an das Vorkommen solcher Infektionen denken, sei es um sie zu verhindern oder um sie zu erkennen und zu behandeln.

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LEFT RETROGRADE CARDIOGRAPHY

In more than 280 patients, Amplatz and his co-workers ascertained that left retrograde cardioangiography was reliable for evaluation of mitral and aortic incompetence, and was also useful in the diagnosis of certain congenital heart lesions. In their hands, the method has had a high order of accuracy. The described technic has been found more reliable and more conclusive than conventional right heart catheterization. While not without risks, the procedure is thought to be definitely warranted in patients in whom corrective surgery is contemplated.

Amplatz, K., Lester, R. G., Ernst, R. and Lillehei, C. W.: "Left Retrograde Cardioangiography: Its Diagnostic Value in Acquired and Congenital Heart Disease," *Radiol.*, 76:393, 1961.

Bronchiolar Carcinoma

A Case Report of Bronchoscopic Observation of Severe Bronchorrhea

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Bronchiolar carcinoma arises in the lung periphery. Liebow[1] has presented strong evidence that the neoplasm arises from the basal cells lining the terminal bronchioles. From these bronchioles, the malignant cells extend into the alveoli and become implanted on the alveolar lining. The tumor consists of many alveoli lined by cuboidal or columnar epithelium with no interruption of the lung structure. Papillary lesions are frequently noted which desquamate readily into the alveoli, and may, through bronchogenic spread, metastasize aerially to other terminal bronchi and alveoli. The cells are usually tall, columnar, but may be cuboidal and rarely may be ciliated. The cells may produce mucin but quite often they do not. The degree of mucus secreting activity of the cells varies greatly and the volume of mucoid sputum varies accordingly. The individual cells may contain large droplets of mucus, and at times, pools of mucus may be present within the lumen of the alveoli and bronchi.

A complete review of reported cases was made by Neuburger and Geever[2] in 1942 (25 cases), Swan[3] in 1949 (61 cases) and Storey, Knudtson and Lawrence[4] in 1953 (145 cases of which 37 were their own).

The symptomatology of bronchiolar carcinoma is as variable as that of other forms of pulmonary malignancy. A considerable number are essentially symptom free with a circumscribed lesion on a chest roentgenogram as the only evidence of pulmonary disease. In the symptomatic cases, cough, expectoration and dyspnea are the most frequent manifestations. A prominant clinical feature in many of these cases is the large volume of mucoid sputum expectorated daily. Cases with several thousand ml. of sputum daily have been reported by Kennamer,[5] by Wood,[6] by Rey and Rubenstein,[7] by Kern, Lewinsky and Curran,[8] and by Storey, Knudtson and Lawrence.[4] The sputum in these cases has been clear mucoid and frothy. Kern, Lewinsky and Curran[8] reported a case with such severe bronchorrhea that depletion of body electrolytes and proteins occurred. However, such extensive degree of bronchorrhea is unusual in cases of bronchiolar carcinoma.

Because this tumor desquamates rather freely, malignant cells can be demonstrated in the sputum by the method of Papanicolaou in about 80 per cent of the patients. As the tumor is peripheral, bronchoscopy fails to reveal a visible lesion unless the tumor has extended to involve the larger bronchi. Although tumor is rarely visible by bronchoscopy, several observers have commented upon the degree of bronchorrhea present at bronchoscopy. Weir reported profuse bronchorrhea on bronchoscopy in

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

one case. Sochocky similary noted large amounts of mucoid secretion on bronchoscopy in one of four cases. However, in the majority of the reports and reviews of bronchiolar carcinoma the statement is usually made that bronchoscopy was negative. The extreme degree of bronchorrhea noted on bronchoscopy of one of our patients with bronchiolar carcinoma is of interest because the secretions prevented effective bronchoscopy; in addition, the rapid formation of the secretions was probably the direct cause of death from asphyxia.

Case Report

A 64-year-old man stevedore was in good health until January, 1959, when he first noted dull, aching substernal pain associated with cough productive of thin sputum. By March, 1959, he raised one cup of thin sputum daily with occasional blood streaking. Chest x-ray film at that time showed a fine mottled infiltration in both lung bases with a more dense, somewhat confluent area in the right mid-lung field. Cough, sputum, shortness of breath, weakness and weight loss gradually progressed. By the time of admission to this hospital on August 19, 1959, secretions were so copious that he had to sleep upright because they flowed from his mouth and nose when reclining. Severe coughing also caused sputum to flow from his mouth and nose.

Physical examination on admission revealed a gaunt, 64 year-old Negro, short of breath at rest, sitting up in bed. There was dullness to percussion over the lower two-thirds of the right lung. Harsh inspiratory and expiratory ronchi were heard throughout the right and at the base of the left lung. Breath sounds were bronchial over the lower two-thirds of the right lung. There was early clubbing of the fingers. Laboratory studies were normal except that the sputum showed many malignant cells with signet-ring formation and mucous production. Chest x-ray film on admission revealed extensive fine mottled infiltration throughout the right lung with some confluence opposite the infraclavicular region and opposite the right hilar region. A similar infiltration was present in the basal portion of the lower lobe of the left lung. On September 2, 1959, more extensive involvement was noted on the left side (Fig. 1).

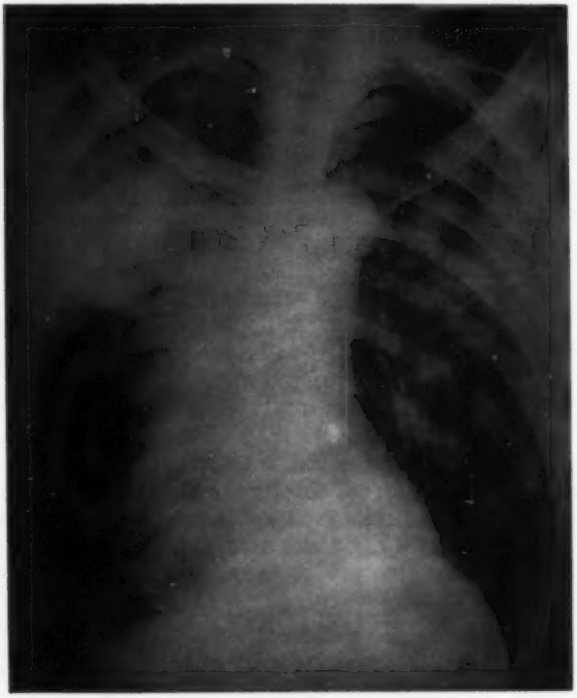

FIGURE 1

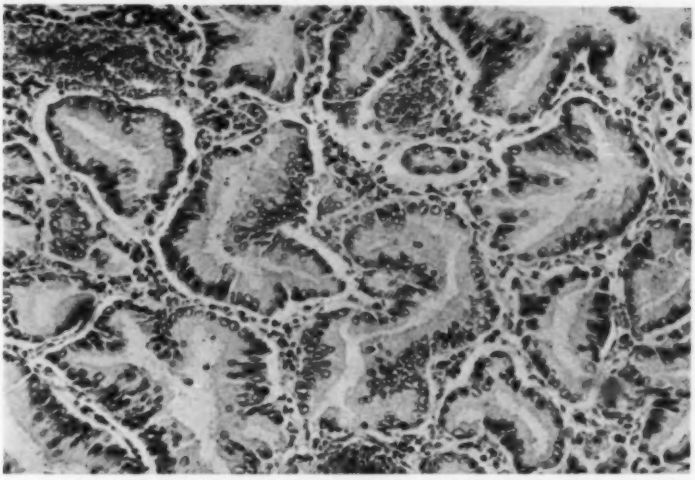

FIGURE 2

On August 24, 1959, when a bronchoscope was inserted into the trachea, it immediately filled with watery secretions. During the five minutes of the bronchoscopic examination, secretions were aspirated almost continuously with a constant flow into the aspirating bottle. The 20 cc. trap was filled within approximately one minute and secretions continued to flow at approximately the same rate. They completely occluded the view. Bronchoscopy was finally abandoned with no satisfactory view of the tracheobronchial tree. Somewhat incomplete sputum measurements on the ward ranged from 480 ml. to 700 ml. per day. The sputum was at all times thin and watery. He died September 7, 1959.

At autopsy the right lung weighed 2,000 gm. and the left lung 1,000 gm. The surface of both lungs had a mottled, greyish-blue appearance. They were firm in consistency. Cut surfaces of the lung had a diffuse granular, greyish-white appearance. On microscopic examination (Fig. 2) all sections of the lung revealed large and small foci of tumor tissue which was made up of tall columnar epithelial cells, most of which lined the alveolar walls, and in many areas formed papillary projections. In many areas the epithelial cells showed mucoid secretions. There was little anaplasia noted in the tumor tissue. Sections taken from the right main stem bronchus presented a typical histologic picture of squamous cell carcinoma with regional lymphnode metastases.

Pathologic diagnosis:

1. Bronchiolar carcinoma of the lung.
2. Epidermoid carcinoma of the right bronchus with metastasis to bronchial lymph nodes.

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X-RAY FILM OF THE MONTH

Edited by Benjamin Felson, M.D.

Clinical Information

The patient is an asymptomatic 17 year-old Caucasian boy with a mass related to the anterior aspect of the left hemidiaphragm found on routine pre-employment chest x-ray film.

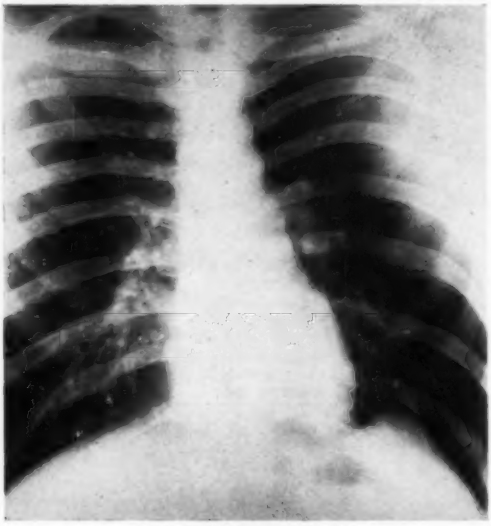

FIGURE 1

Diagnosis: PERICARDIAL CYST

This is thought to represent a pericardial cyst, uncommon in this location. Three-fourths of pericardial cysts are found on the right side.[1]

The differential diagnosis of the demonstrated mass is essentially that of a supradiaphragmatic mass. Intradiaphragmatic tumors are quite rare, there having been only 67 cases reported in the literature.[2] Supradiaphragmatic masses are produced by lesions of *the pleura*—cyst, neoplasm, loculated effusion, fibrin ball, loculated empyema, pericardial fat pad; *of the lung*—lobar sequestration, cyst, abscess, neoplasm; *of the pericardium*—cyst, neoplasm; *of the esophagus*—enteric cyst, reduplication, neoplasm; and *of the thoracic wall*—neoplasm, infection.

Diagnostic pneumoperitoneum is a simple and useful procedure in excluding herniation of subdiaphragmatic structures into the thorax (Fig. 2). Pneumoperitoneum may be combined with diagnostic pneumothorax to further define intradiaphragmatic or supradiaphragmatic lesions.

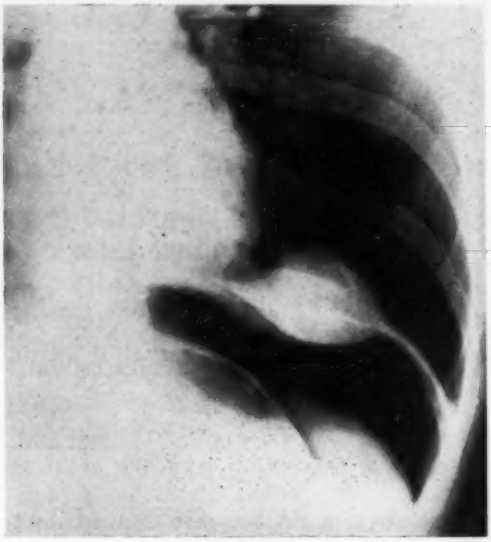

FIGURE 2

At thoracotomy, a cyst was found in the pleural space, attached by a fibro-adipose pedicle to the adjacent pericardium and diaphragmatic pleura anteriorly. Grossly, the specimen consisted of a 9 x 5 cm. smooth, thin-walled, bi-lobed cyst containing watery fluid. Microscopically, a fibrous cystic wall with mesothelial lining was found, with no evidence of inflammatory process or malignancy.

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The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with a brief history. Please submit material to: Benjamin Felson, M.D., Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

SECTION ON CARDIOVASCULAR DISEASES

Transfer of Coronary Ostia by "Triangulation" in Transposition of the Great Vessels and Anomalous Coronary Arteries*

A Preliminary Report

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Complete correction of transposition of the great vessels has commanded the attention of numerous cardiovascular groups in this country. Many hours of intensive thought and investigation have been expended on its behalf. The final answer still remains unsure, and it is highly essential that every possible avenue of solution be explored. This presentation describes an operative procedure developed in the experimental laboratory which may be applicable to the problem, and which may also be applicable to surgical treatment of anomalous coronary arteries.

Before a satisfactory answer can be found, several criteria must be fulfilled: (1) *the proposed operative procedure should be applicable to the newborn period.* Study of the natural history of transposition indicates that a large number are dead within the first six months of life. Before adequate salvage can be attained, the operative procedure must be applicable almost immediately after birth; (2) *there must be adequate provision for growth of the patient.* In spite of any initial operative successes, if growth of the patient to adulthood is not permitted, the ultimate result will be poor; (3) *pulmonary hypertension should be alleviated.* So many transpositions have increased pulmonary arterial pressure and associated hypertrophic changes in the pulmonary arterioles that these changes will certainly affect the long term results of any operative procedure. Anything that can be done to reverse them will surely improve operative mortality and morbidity; (4) *the proposed operative procedure should be technically suited to the majority of transposition defects that might be encountered.* These types are numerous and have been described in other communications.[1-3] If most of them cannot be corrected by a proposed operative procedure, its usefulness will be limited.

Two major approaches to the surgical correction of transpositions have evolved. In one group of operative procedures, the transposition of the outflow tracts is accepted, and correction is achieved in whole or in part,

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by altering venous inflow to the heart.[4-6] In the other group of operative procedures, attempts have been made to alter the outflow tracts themselves.[7,8] The latter group is extremely attractive because of its greater potential efficiency. However, correction of the outflow tracts has been frustrated by difficulty in transferring the coronary arteries. Techniques for extracorporeal circulation have now been developed to the point where transfer of the ascending aorta and the main pulmonary artery is feasible. Thus far, the most difficult technical problem has been successful transfer of the coronary arteries along with the base of the aortic arch. It was our purpose to attempt once again to find a satisafctory method for transferring the coronary arteries from the pulmonary to the systemic outflow tracts. The anatomy of the coronaries in transposition of the great vessels was reviewed and the method described below was devised.

Surface Anatomy of the Coronary Arteries in Transpositions

Examination of autopsy specimens as well as patients with transpositions who were operated upon by partial venous correction indicates remarkable consistency in the site and mode of origin of the coronary arteries. The aorta, of course, arises from the anterior ventricle in transpositions and is usually directly in front of the pulmonary artery, which arises from the posterior ventricle (Figure 1). These two vessels are in close proximity to each other, even when the relationship of the aorta to the pulmonary artery is not entirely anterior-posterior, or when they are of different sizes. This is not surprising, since they arise from the same primitive vascular tube. Their identical embryologic origin also fixes the position of their valve commissures and the ostia of the coronary arteries. The two central commissures—the posterior commissure of the aortic valve and the anterior commissure of the pulmonary valve —are consistently found directly opposite each other (vis-a-vis), and the

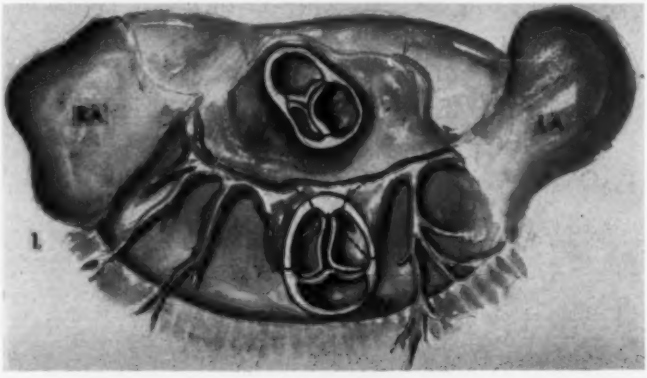

FIGURE 1: Surface anatomy of the coronary arteries in transpositions. The right and left coronary ostia arise from the posterior aspect of their respective sinuses of Valsalva, near the posterior commissure of the aortic valve (*i.e.*, valve of the outflow tract of the right ventricle [RV]). They are in close proximity to the outflow tract of the left ventricle (LV). Triangulation of the sinuses of Valsalva bearing the coronary ostia provides a large segment of the aortic wall which can be used for anastomosis to the outflow tract of the left ventricle (note dotted lines).

sinuses of Valsalva that bear the coronary ostia are consistently found on either side of the posterior commissure of the aortic valve.

Furthermore, the coronary ostia usually arise from the rear of the sinuses of Valsalva, so that they are close to the posterior commissure of the aortic valve and the posterior wall of the aorta itself. This places them in close proximity to the main pulmonary artery, or, more important, the outflow tract of the left ventricle. Transfer of the coronary arteries to the outflow tract of the left ventricle seems feasible, if severe twisting can be prevented. The least amount of twisting was found to occur when the coronary ostia were transferred independently of the ascending aorta. By excising triangular segments of the sinuses of Valsalva containing the coronary ostia, and allowing them to fall into place on to the outflow tract of the left ventricle (Figure 2), minimal rotation of the coronary arteries occurred and their patency was not diminished. Following this maneuver, the ascending aorta could be anastomosed to the outflow tract of the left ventricle with ease. In fact, disparity in size between the aorta and the outflow tract of the left ventricle could be corrected by tailoring the triangular segments to fit the base of the ascending aorta. The pulmonary artery could then be attached to the outflow tract of the right ventricle, added length being obtained by mobilization of its main branches and division of the patent ductus arteriosus.

This method has been called "triangulation" of the sinuses of Valsalva. It seems applicable not only to transpositions with the usual coronary arterial patterns, but also to those with aberrant coronaries arising from a single ostium. Of equal importance is the fact that it seems applicable also to cases of primary anomalous coronary arteries, where no transposition defect exists. These anomalous coronary arteries, in the small

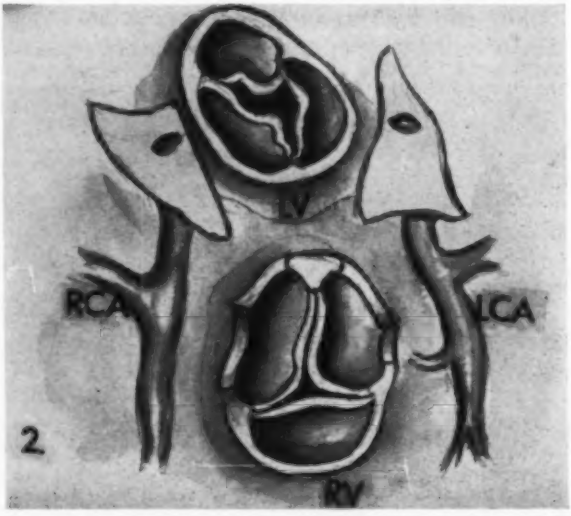

FIGURE 2: The triangular segments of the wall of the sinuses of Valsalva are rotated onto the outflow tract of the left ventricle (LV). The integrity of the aortic and pulmonary valves has not been disturbed. The main trunks of the coronary arteries (LCA and RCA) are patent.

series of necropsied cases that we have had the opportunity to study, also arise close to the central commissure of their parent vessel and in close proximity to the opposite outflow tract. There is no apparent technical reason why they cannot be transferred by triangulation to the left ventricular outflow tract.

Operative Procedure for Transposition of the Great Vessels

Figures 1 through 4 illustrate the operative maneuvers for transferring the aorta, the pulmonary artery and the coronary arteries by triangulation. A vertical midline incision is made through the body of the sternum and the superior and inferior vena cavas are cannulated in the usual manner for extracorporeal circulation. The femoral artery is used for entry into the arterial system. The aorta and the pulmonary artery are dissected so that they are mobile and move independently of one another. It is usually necessary to mobilize the right and left pulmonary arteries and to divide the patent ductus arteriosus to allow adequate mobility of the pulmonary artery. After the patient is in balance with the heart-lung machine, coarctation clamps are applied to the aorta and the pulmonary artery, and these vessels are divided away from

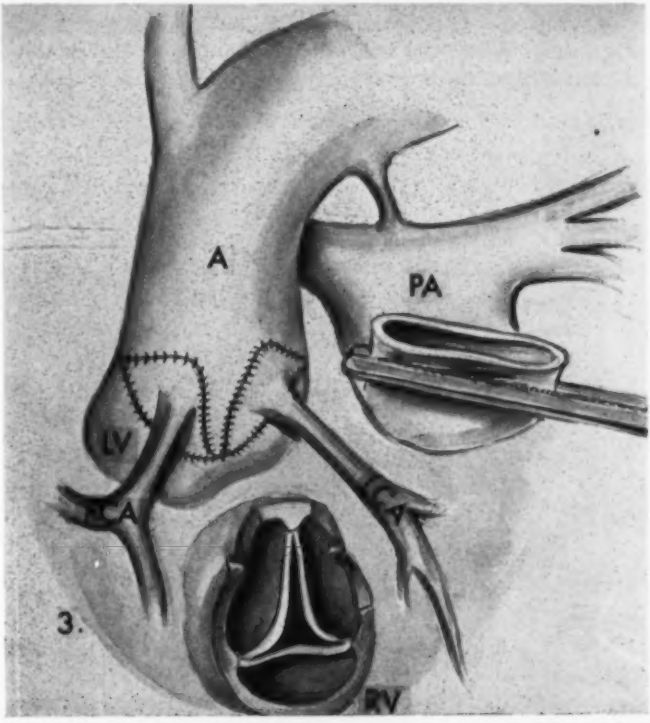

FIGURE 3: The triangular segments have been anastomosed to the outflow tract of the left ventricle. The ascending aorta (A) has been anastomosed to complete the new outflow tract of the systemic circulation. The pulmonary artery (PA) has been mobilized and is being moved down to the outflow tract of the right ventricle. At this point, the patent ductus arteriosus may have to be divided to provide increased mobility of the pulmonary artery.

their respective outflow tracts. Each sinus of Valsalva containing the ostium of a coronary artery is excised in such a way that a generous portion of the aortic wall is removed but no damage is done to the cusps of the valve leading from the outflow tract of the right ventricle (Figure 2). This segment is triangular in shape with the apex inferior. It is allowed to rotate onto the outflow tract of the left ventricle and sewn into place (Figure 3). Both the right and left coronary arteries are transferred in this manner. They have to be cleared from the surrounding epicardial fat in order to allow adequate mobility, but after that is done they only have to be rotated about 45 degrees to reach the proper position onto the outflow tract of the left ventricle. This rotation does not occlude the coronaries and there is no apparent interference with coronary flow either in systole or diastole.

After the triangular segments are affixed to the outflow tract of the left ventricle, the ascending aorta is attached. When this has been completed, the coarctation clamp on the ascending aorta is released, allowing perfusion of the coronary arteries. Since transfer of the coronary arteries and the aorta can be accomplished well within 25-30 minutes, there is little danger of anoxia to the myocardium. After perfusion of the coronary arteries has been initiated, the pulmonary artery may be transferred without haste to the outflow tract of the right ventricle (Figure 4). When the operation is completed and adequate heart action is restored, extracorporeal circulation is discontinued.

Operative Procedure for Transpositions with Aberrant Coronary Arteries

Our preliminary studies show that a significant number of transpositions have both coronary arteries arising from a single coronary ostium.

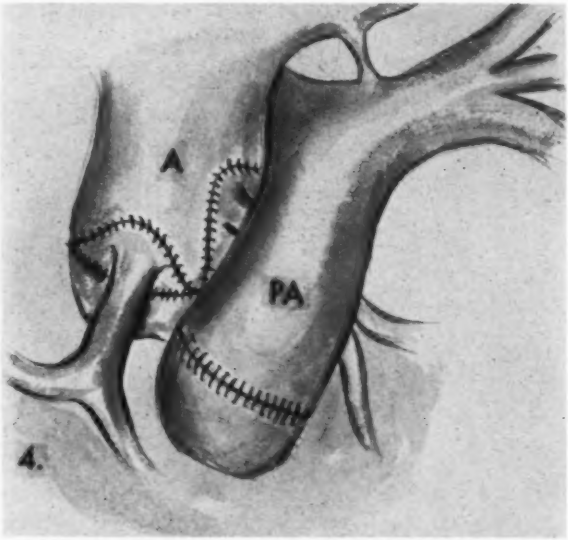

FIGURE 4: Completion of the outflow tract correction by suturing the pulmonary artery to the outflow tract of the right ventricle. The coronary arteries are not rotated to the point of occlusion of their main trunks. They lie in satisfactory position on either side of the main pulmonary artery.

The usual pattern is shown in Figure 5. The right and left coronary arteries arise from a single sinus of Valsalva and have a single ostium. The left coronary artery extends behind the pulmonary artery to supply the left side of the myocardium. Although this type of single coronary origin permits transfer of the coronary circulation along with the base of the aorta, triangulation of the sinus of Valsalva may prove useful for improving the patency of the coronary arterial lumen or the position of the coronary ostium in the left ventricular outflow tract. Furthermore, note that in this particular illustration, as in so many transpositions, there is an over-riding pulmonary artery with disparity in the sizes of the outflow tracts of the right and left ventricles. After the common coronary ostium is "triangulated" out of the parent sinus of Valsalva and transferred to the outflow tract of the left ventricle, it can be utilized to compensate for the disparity in sizes of the aorta and the left ventricular outflow tract.

Operative Procedure for Anomalous Coronary Arteries

It is highly probable that triangulation may find its greatest usefulness in transfer of anomalous coronary arteries without transposition defects. Review of specimens in which one coronary artery arose from the normally placed aorta (left ventricular outflow tract), while the other

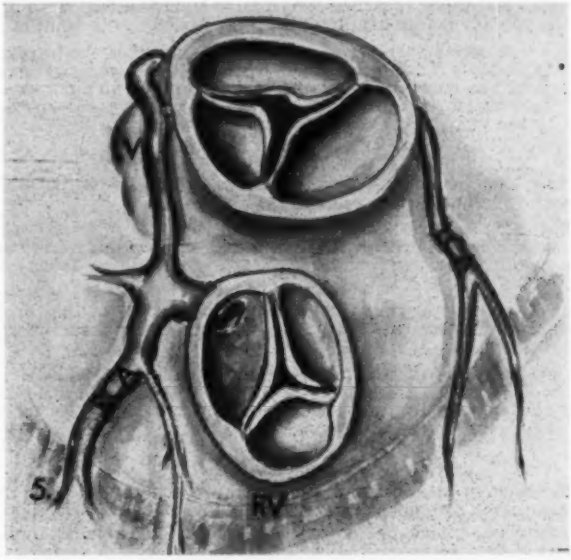

FIGURE 5: Diagram of the situation often encountered in transpositions with aberrant coronary arteries. All the coronary circulation arises from a single coronary ostium. The left coronary artery extends behind the outflow tract of the left ventricle before approaching the anterior aspect of the myocardium. It is apparent that the wall of the sinus of Valsalva bearing this common coronary ostium can be triangulated and transferred to the outflow tract of the left ventricle without undue rotation of the main coronary trunks. The triangular segment of the wall of the sinus of Valsalva can also be used to compensate for the disparity in size between the outflow tract of the left ventricle and the outflow tract of the right ventricle shown here. This disparity in size results when over-riding of the pulmonary artery is an integral part of a particular transposition complex.

arose from the pulmonary artery (right ventricular outflow tract) indicated that the relationship of the central commissures described in Figure 1 obtains in these patients as well. The anomalous coronary ostium is close to the posterior, central commissure of the pulmonary artery, and is indeed in close proximity to the outflow tract of the left ventricle. It would seem a simple technical procedure, after extracorporeal circulation has been established, to excise the ostium of the anomalous coronary artery by triangulation, rotate it 45 degrees onto the outflow tract of the left ventricle and insert it into the base of the ascending aorta where it belongs.

Discussion

Doubt has been raised by some investigators as to the potential efficacy of total correction of transposition defects by altering their outflow tracts. It is pointed out that the heart adapts very early to the fact that the pulmonary artery originates from the left ventricle and the aorta arises from the right venricle. Catheterization studies, although too few to be conclusive, suggest that, after adaptation, the venricles may not be able to withstand being transferred to what is considered a normal arrangement. This is particularly true of the left ventricle, which in transpositions is required to work only against pulmonary resistance. There is serious doubt in the minds of some investigators that such a left ventricle could withstand the sudden increased work load imposed by attaching it to the ascending aortic arch.

This applies, however, only to some transposition complexes, where there is no interventricular septal defect or only a very small one. There are other types of transposition complexes—e.g. Taussig-Bing complexes—where both ventricles are hypertrophied and where the left ventricle is probably quite capable of working against systemic arterial resistance. Furthermore, many transpositions become dangerously ill early in life, possibly before adaptation has proceeded to the point of no return.

Since there are so many varieties to be corrected and since the ideal operative procedure for transpositions is still not defined, it seems desirable to explore every possible avenue of solution. The maneuvers described above are presented not as a final answer, but because they might be of interest to investigators working on the problem of transposition of the great vessels or of anomalous coronary arteries.

SUMMARY

1. The surface anatomy of the coronary arteries in transposition of the great vessels and of anomalous coronary arteries has been reviewed.

2. Based on this surface anatomy, operative maneuvers for correction of the outflow tract in transpositions with or without aberrant coronary arteries have been described as they were developed in the experimental laboratory and on fresh necropsy specimens.

3. A similar operative procedure, involving "triangulation" of the sinus of Valsalva, has been described for correcting anomalous coronary artery occurring in the absence of the transposition defect.

4. On the basis of these studies, triangulation of the sinus of Valsalva seems technically feasible and permits transfer of the coronary ostia from one outflow tract to the other without significant rotation of the main trunks of the coronary arteries and without damage to the aortic or pulmonary valves.

RESUMEN

La tranferencia de la ostia coronaria en la transposición de los grandes vasos y de las arterias coronarias anómalas. Informe preliminar.

1. La superficie anatómica de las arterias coronarias en la transposición de los grandes vasos y de las coronarias anomalas es objeto de esta revisión.

2. Basandose en esa anatomía se han descrito procedimientos operatorios para corregir el paso del flujo al exterior en las transposiciones con o sin arterias coronarias aberrantes y se han llevado a cabo experimentalmente y en especimenes frescos de autopsias.

3. Un procedimiento similar operatorio incluyendo la "triangulación" del seno de Valsalva se ha descrito para corregir las coronarias anómalas en ausencia de defecto de transposición.

4. Basandose en estos estudios la triangulación del seno de Valsalva parece tecnicamente factible y permite la transferencia de las ostias coronariae de un sentido del flujo hacia otro sin rotación significante de los troncos principales de las arterias coronarias y sin daño de las valvulas aorticas o pulmonares.

RESUMÉ

1. La surface anatomie de l'artere coronaire dans la transposition du grand vaisseau et de l'artere coronaire anomalous a ete reviser.

2. Basé sur la surface de l'anatomie, maneuvres pour correction de la voie du courant en transposition avec ou sans "aberrant" artère coronaire ont ete décris comme ils ont ete developes dans le laboratoire experimental et sur de frais specimens.

3. Une semblabe procedure d'operation impliquant triangulation de la sinus de valsalva, a ete decris pour correction de L'artere coronaire anomalous, arrivant dans l'absence du defait de la transposition.

4. Sur la base des etudes, triangulation de la sinus valsalva est techniquement faisable et permet le transfer de l'ostia coronaire de la voie du courant a une autre sans rotation signifiquante de l'arbre principal de l'artere coronaire et sans dommage aux soupapes pulmonaires aortic.

ZUSAMMENFASSUNG

Verlegung der Coronarostien durch "Triangulation" bei Transposition der grossen Gefässe und anormalen Coronararterien: Vorläufiger Bericht.

1. Die Anatomie der Coronararterien bei Transposition der grossen Gefässe und bei anormalen Coronararterien wird besprochen.

2. Auf der Basis dieser anatomischen Verhältnisse wurde ein operatives Vorgehen zur Korrektur de rAusflussbahn bei Transpositionen mit oder ohne aberrierende Coronararterien beschrieben. Dies wurde exsperimentell im Laboratorium und an frischem Autopsie-Material entwickelt.

3. Ein ähnliches operatives Vorgehen mit "Triangulation" des Valsalvasinus wurde beschrieben um anormale Coronararterien ohne Transpositionsdefekt zu korrigieren.

4. Auf der Grundlage dieser Untersuchungen erweist sich die Triangulation des Valsalvasinus als technisch möglich und erlaubt die Überführung der Coronarostien von einer Ausflussbahn zur anderen ohne wesentliche Rotation der Hauptäste der Coronararterien und ohne Schaden für die Aorten- und Pulmonalisklappen.

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SURGICAL TREATMENT OF ASTHMA

Right pulmonary plexus resection has been carried out in 16 patients for the treatment of asthma. The results of this procedure have been assessed in the 13 patients who had this operation more than a year ago. All except one had had steroid therapy before operation, and in 14, this was continued or restarted after operation. One patient died seven months after his operation; of the remaining 12, six are "much improved," four are "improved," and two are "no better." The results of surgery seem to justify its consideration in patients severely disabled despite steroid therapy.

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Pulmonary Function in Cardiac Disease[1,2]

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Introduction

It has been well established that pulmonary function can be altered by cardiac disease.[1] Conversely, pulmonary pathology may result in abnormal cardiac function and anatomy. Pulmonary function testing offers a simple method of quantitating and following these changes. The purpose of this paper is to illustrate the value of such measurements in cardiovascular disease. This is particularly useful in evaluating the effects of various modalities of therapy.

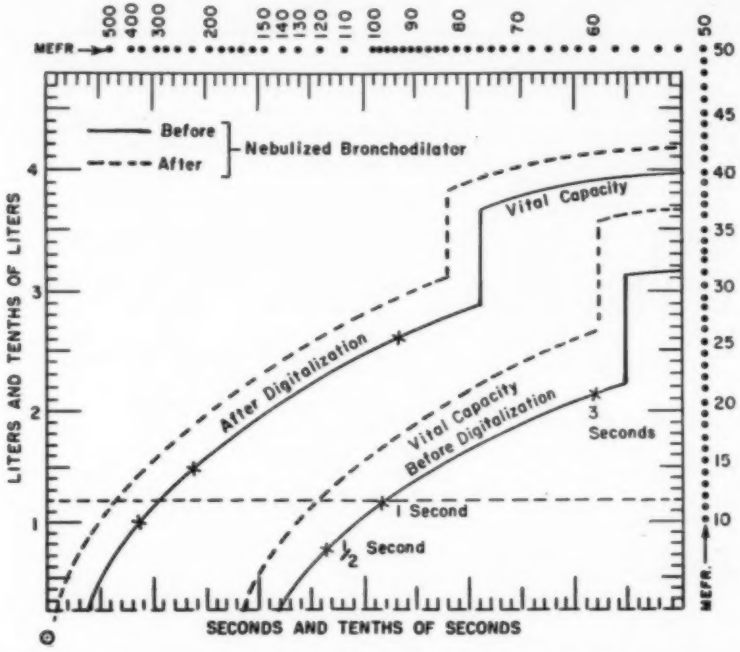

FIGURE 1: Ventilographic response on the Vitalor of a patient with cor pulmonale and "obstructive" emphysema to digitalization before and after nebulized bronchodilator therapy. (The vertical lines represent volume only—explanation has been previously described.[1])

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[1]Presented at the 26th Annual Meeting, American College of Chest Physicians, June 8-12, 1960, Miami Beach, Florida.

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Procedure

The parameters selected for study on patients in this series were: a total and timed vital expiratory capacity of the lung and the maximal expiratory flow rate, as obtained by the bellows vital capacity apparatus (the Vitalor‡). Arterial oxygen and carbon dioxide studies also were carried out.

The patients studied were adult men in frank congestive failure. They were studied on the basis of either right or left heart failure. All testing was done in the standing position, when possible.

These patients were tested before and after various forms of treatment. The drugs used were: digitalis, aminophyllin, hydrochlorothiazide, isoproterenol, and prednisone.

In addition, circulation times, venous pressures, electrocardiograms and posteroanterior, right anterior oblique and left anterior oblique chest x-ray films were used in evaluating the clinical status of the patient. All of this information was correlated with the preliminary function tests.

Results and Discussion: Right Ventricular Failure

Eleven patients in right heart failure were studied by means of the Vitalor. Failure in these patients was caused mainly by cor pulmonale resulting from obstructive emphysema, inactive tuberculosis, pulmonary fibrosis, chronic empyema, silicosis, and Boeck's sarcoidosis. Ventilatory studies in cor pulmonale were not as dramatic as in failure. This finding is to be expected, since the edema of right ventricular failure usually is found in the abdominal viscera and lower extremities, rather than in the

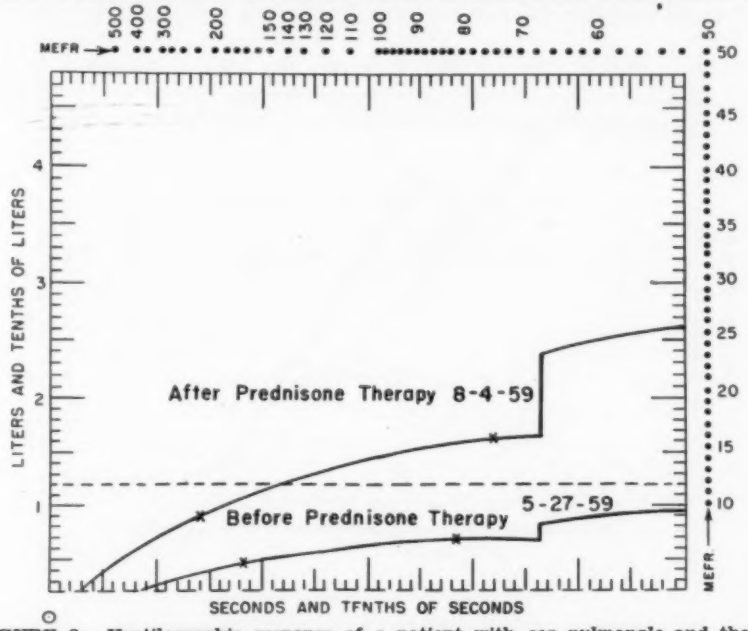

FIGURE 2: Ventilographic response of a patient with *cor pulmonale* and therapeutically resistant anasarca, treated with adrenocortical steroids (prednisolone).

‡The apparatus used in this paper was graciously furnished by the McKesson Appliance Company, Toledo, Ohio.

lungs. This may explain the symptomatic improvement seen when patients with chronic left ventricular failure develop right ventricular decompensation. It should be pointed out that the interpretation of abnormal results obtained in pulmonary function testing is made more difficult by the presence of coexistant lung disease. Therefore, this testing is of limited diagnostic value here. However, the patient with "obstructive" or "restrictive" lung disease who develops right ventricular failure usually shows a further decrease in total vital capacity.[2] This may be due to progressive bronchopulmonary disease or the development of superimposed left ventricular decompensation. Figure 1 illustrates the response before and following the use of digitalis and isoproterenol where the total vital capacity increased as usually occurs after the cardiac therapy[3] in this type of case with the maximum expiratory flow rate and the timed vital capacity remaining low.

Figure 2 illustrates pulmonary function studies done on a patient with severe cor pulmonale after irretractable failure. Following prednisone therapy, there was a marked diuresis resulting in a dramatic improvement in the clinical cardiac status and in the pulmonary status as determined by the three ventilatory parameters measure by the Vitalor. This is probably because the steroid therapy reduced some of the bronchial spasm, bronchial edema, and bronchial inflammation (in addition to possible direct cardiovascular and renal action) thus relieving part of the right ventricular strain and hypoxia, increasing more adequate air exchange, and thereby also decreasing the work of breathing.

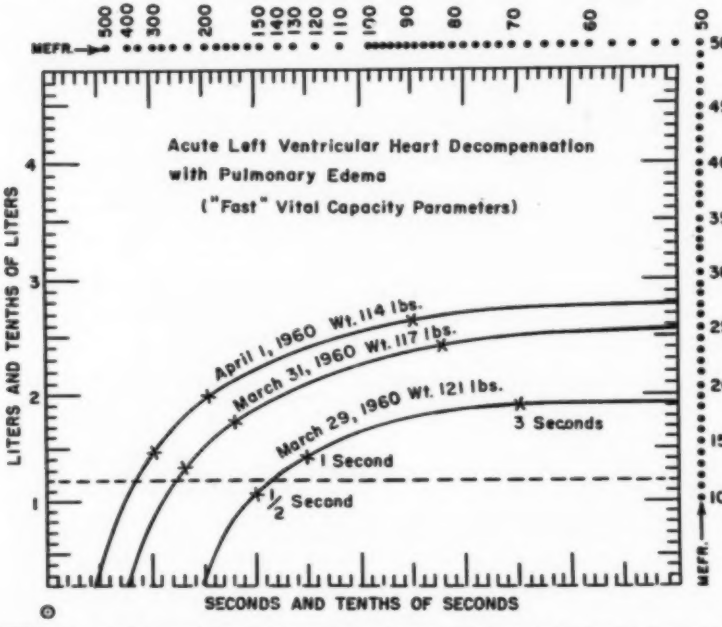

FIGURE 3: Serial ventilographic studies of a patient with left ventricular failure under therapy.

We also have found that blood arterial gas studies[3] offer a better correlation with right ventricular failure than do ventilatory studies, and also are more useful in evaluating the response to therapy.

Left Ventricular Failure

The lungs, by virtue of their position in the circulation, have long been recognized as a sensitive indicator of inadequate performance of the left ventricle.

The 18 patients in left ventricular failure tested in this study demonstrated a marked reduction in the total vital capacity and to a lesser (often minimal) extent of the timed (forced) vital capacity and the maximum expiratory flow rate (Fig. 3). Why this occurs is readily understood.

Von Basch in 1891 described the rigidity and stiffness of the lungs in heart failure ("Lungenstarre") with the subsequent observation revealing the dyspnea in heart disease, particularly in left ventricular failure and in decompensated mitral stenosis, is as closely related to lung compliance as any other single observation. Since compliance (*i.e.*, ratio of change in lung volume to change in transpulmonary pressure: a low value signifying increased lung rigidity) is shown to vary directly with the total vital capacity, it is apparent that reduction in compliance, diminished vital capacity, and dyspnea in congestive failure are closely related. Figure 4 illustrates the direct linear correlation between lung compliance and the total vital capacity.

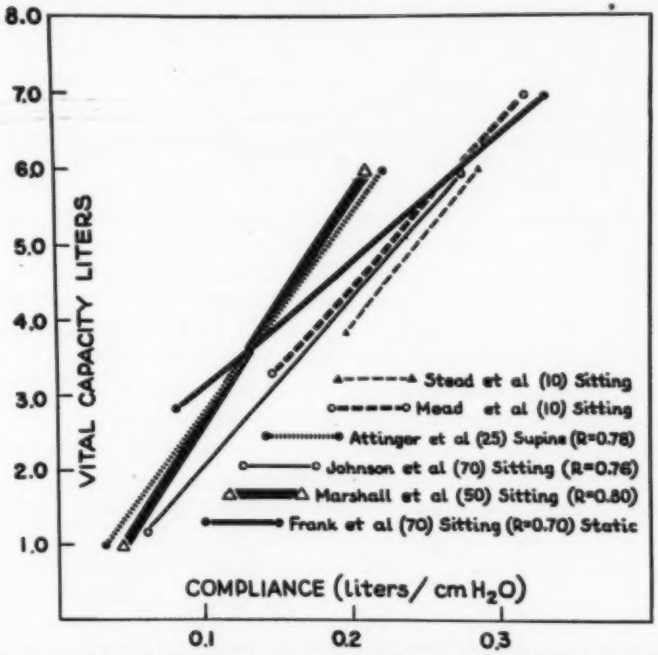

FIGURE 4: Graphic demonstration of direct linear relationship between the total vital capacity and pulmonary compliance. (Courtesy of William F. Miller, M.D., Dallas, Texas.)

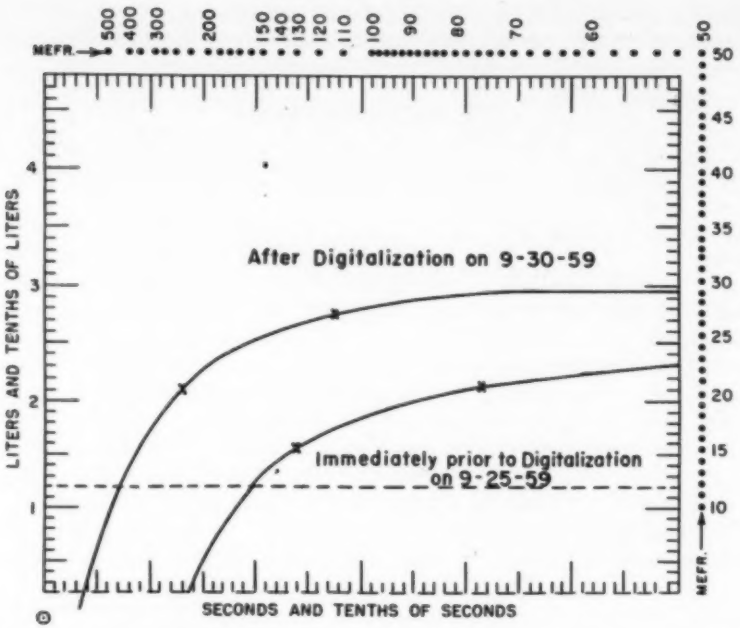

FIGURE 5: Serial ventilographic changes obtained prior to digitalization for left ventricular failure and then five days later.

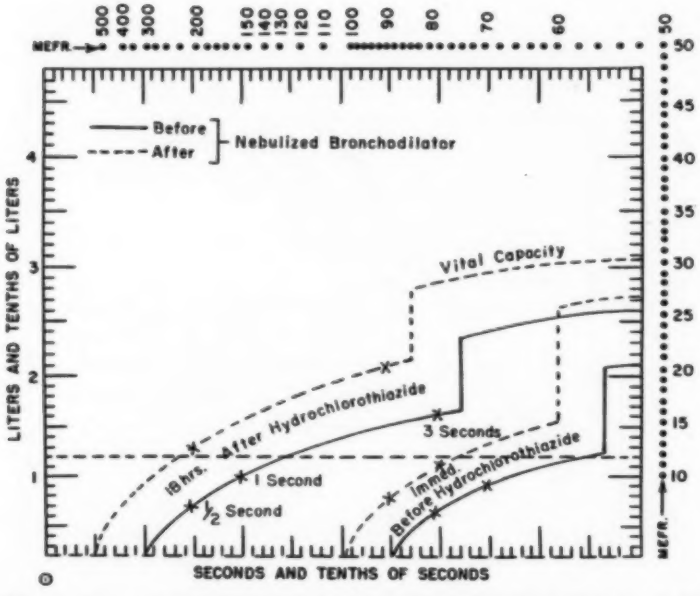

FIGURE 6: Response of patient to hydrochlorothiazide therapy before and after nebulized bronchodilator administration.

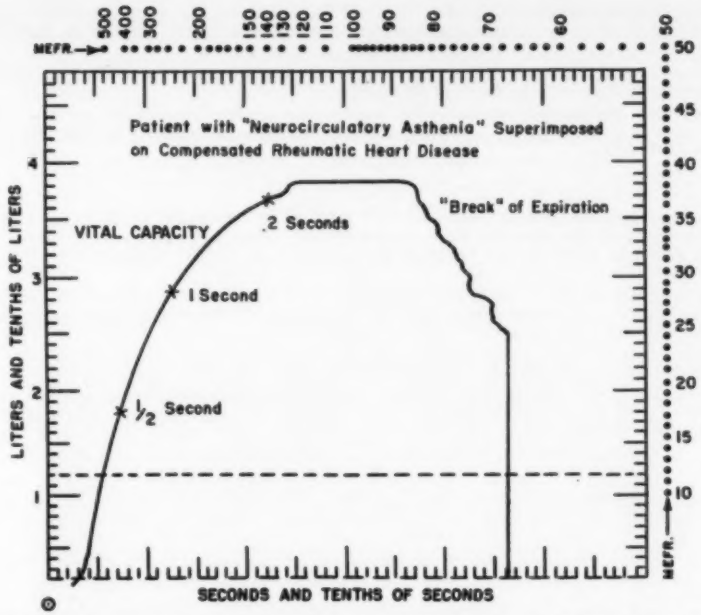

FIGURE 7: Demonstration of the value of the *expiratory ventilagram*[1] in a cardiac patient with a superimposed cardiac neurosis with hyperventilation syndrome.

Thus, the total vital capacity may be inversely proportional to the degree of pulmonary congestion. Because of this, pulmonary function testing offers the practitioner a simple and extremely useful tool for the evaluation of the response of left ventricular failure to the various modes of therapy. This is demonstrated in Figure 5 with an improvement in the three parameters measured. This was also true following the use of nebulized isoproterenol as demonstrated in Figures 1 and 6. The effect of an oral diuretic, hydrochlorothiazide, also is demonstrated in Figure 6 in an individual with left ventricular failure. This figure also illustrated the importance of bronchospasm reversible by nebulized bronchodilator therapy which may be present in certain cases of left ventricular failure associated with bronchial edema due to infection or with the fluid retention or bronchospasm associated with the pulmonary edema.

In addition, pulmonary function is a valuable tool differentiating the cardiac patient with a superimposed cardiac neurosis with hyperventilation syndrome from one in left ventricular failure (Fig. 7).

In the dyspneic patient with thyrotoxicosis, anemia, obesity, or neurosis, normal pulmonary function testing may help eliminate congestive failure as a cause. Normal function in a resting patient, however, does not necessarily mean that failure is not the cause of the symptoms which occur only on effort.

SUMMARY

1. Measurements of the (forced) total and timed expiratory vital capacities and maximum expiratory flow rates have been made in 11 patients with obvious right ventricular failure and in 18 with left ventricular failure.

2. Pulmonary ventilation studies were of limited value in right ventricular failure except in following the response to therapy. Arterial gas studies were more informative here.

3. However, ventilation tests were a sensitive indicator of incipient or frank left ventricular failure and its response to therapy.

4. Normal parameters obtained on pulmonary ventilation testing as described in this paper were helpful in differentiating acute left ventricular failure from other causes of dyspnea.

RESUMEN

1. La medida de la expiración forzada total y por segundos de la capacidad vital asi como la máxima tasa del flujo expiratorio se llevaron a cabo en 11 enfermos que tenian evidente insuficiencia ventricular derecha y en 18 con insuficiencia ventricular izquierda.

2. Los estudios de la ventilación pulmonar fueron de valor limitado en la insuficiencia ventricular derecha exceptuando despues de la respuesta al tratamiento. Los estudios del gas arterial fueron mas informativos en ese caso.

3. Sin embargo las pruebas ventilatorias fueron de valor limitado en la insuficiencia incipiente o franca ventricular izquierda y su reespuesta al tratamiento.

4. Los parámetros normales obtenidos en las pruebas ventilatorias según se describen en este trabajo fueron útiles para diferenciar la insuficiencia ventricular izquierda aguda de otras causas dedisnea.

RESUMÉ

1. Des mesures de la capacité totale et de la capacité vitale ainsi que de la ventilation maximale ont été faites chez 11 malades présentant une atteinte ventriculaire droite évidente, et chez 18 malades avec atteinte ventriculaire gauche.

2. Les études de la ventilation pulmonaire furent de valeur limitée dans l'atteinte ventriculaire droite, sauf pour suivre la réponse à la thérapeutique. L'étude des gaz artériels donna plus d'informations dans ce cas.

3. Cependant, les tests de ventilation donnèrant des indications sensibles de l'atteinte naissante ou franche du ventricule gauche et de sa réponse au traitement.

4. Des paramètres normaux obtenus par les tests de ventilation pulmonaire, comme il est décrit dans cet article, furent utilisés pour différencier l'atteinte aiguë du ventricule gauche des autres causes de dyspnée.

ZUSAMMENFASSUNG

1. Es wurden Messungen der (forcierten) totalen und Sekunden-Expirationsluft sowie der maximalen expiratorischen Ausströmungswerte bei 11 Kranken mit Insuffizienz des rechten Ventrikels und bei 18 Kranken mit Insuffizienz des linken Ventrikels vorgenommen.

2. Lungenventilationsproben waren von begrenztem Wert bei Insuffizienz des rechten Ventrikels, abgesehen von dem Erkennen der Reaktion auf die Therapie. Arterielle Gasanalysen gaben bessere Informationen.

3. Jedoch waren Ventilationsprüfungen ein empfindlicher Indikator für eine beginnende oder offenbare Linksinsuffizienz und ihre Reaktion auf die Behandlung.

4. Die normalen Parameter-Werte aufgrund von Lungenventilations-prüfungen, wie sie in dieser Mitteilung beschrieben werden, waren eine gute Hilfe zur Differenzierung eines akuten Linksversagens gegenüber anderen Ursachen von Kurzetmigkeit.

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The Role of Aortography in the Diagnosis and Management of Dissecting Aneurysms of the Aorta

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The availability of surgical techniques for the treatment of dissecting aneurysms of the aorta[3] has created a need for the accurate preoperative diagnosis of the presence and extent of this lesion.

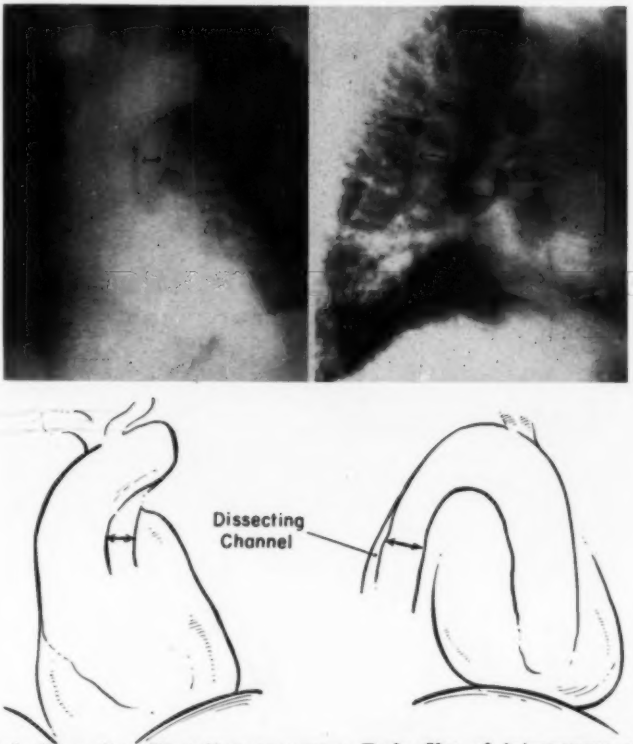

FIGURE 1 (Case 1): Dissecting aneurysm. Early film of intravenous aortogram showing double lumen beginning distal to the origin of left subclavian.

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This work was supported in part by grants from the United States Public Health Service (H-4234, H-4335), the Squibb Institute for Medical Research, and Winthrop Laboratoriees, Inc.
†Established investigator, American Heart Association.
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The diagnosis is frequently suggested by a history of hypertension and the sudden onset of severe tearing chest pain which radiates posteriorly to the interscapular space and is not relieved by narcotics. The index of suspicion is increased by findings of an aortic diastolic murmur, decreased femoral or radial pulses, and paraplegia. A widened mediastinal shadow in the chest x-ray film, with or without evidence of fluid in the pleural or pericardial spaces, further suggests this diagnosis.

Various angiographic techniques have been utilized in an effort to confirm the diagnosis and to accurately delineate the dissecting process. The use of angiocardiographic techniques for the demonstration of lesions of the thoracic aorta was first suggested by Steinberg in 1940.[9] Eight years later, Paulin and Davis[8] first successfully demonstrated a dissecting aneurysm with this technique. In 1955, DeBakey[3] stated, "The most valuable method of diagnosing dissecting aneurysm of the aorta roentgenographically is by angiocardiography," and presented three cases so diagnosed. Similar techniques have more recently been employed to diagnose this condition by several other investigators.[3,7,10]

Retrograde aortography via the femoral artery may be utilized to demonstrate the dissection,[4,11] but carries the risk of creating additional

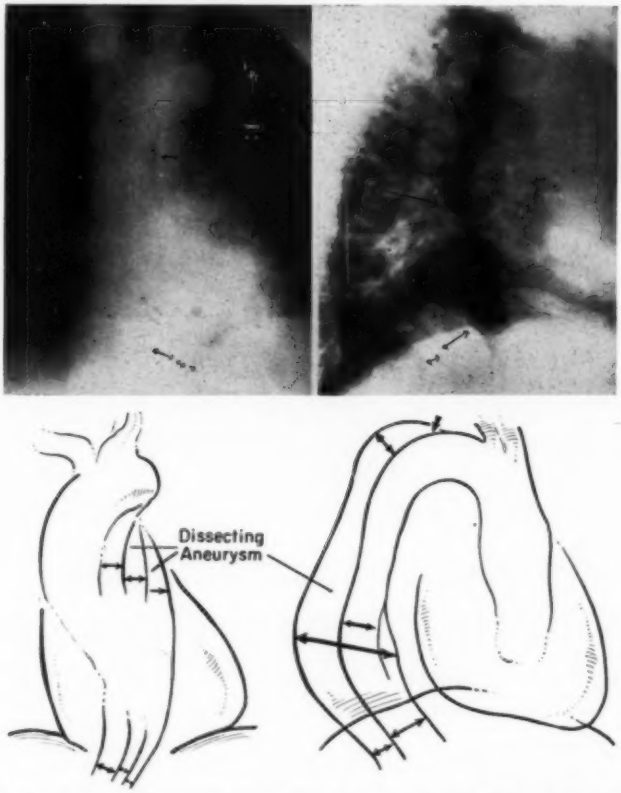

FIGURE 2 (Case 1): Same case as Figure 1—later film—three separate lumina are visible in both the AP and lateral views. These extend below the diaphragm.

difficulties in a vessel which may already be involved by the dissecting process. A forward (intravenous) approach appears to be safer and is equally informative. It is the purpose of this communication to present five cases of dissecting aneurysm of the aorta diagnosed by intravenous aortography and to discuss the implications of angiographic studies upon the surgical treatment of this condition.

Case Reports

Case 1, H.B.: This 75 year-old white man was admitted to the University of Minnesota Hospitals on March 19, 1959. Approximately 36 hours prior to admission, while sitting quietly at home, the patient experienced the sudden painless onset of numbness and paralysis of his lower extremities. Shortly thereafter, he noted the onset of anterolateral and posterior left chest pain of moderately severe character, which continued intermittently through the night. By the following morning, the chest pain was less severe and the numbness and paresis of his lower extremities had disappeared. X-ray films taken in another hospital at this time revealed some widening of the mediastinum. He was transferred to the University Hospitals for further evaluation.

On admission, the blood pressure was 135/70, the pulse 100, respirations 22 per minute. Heart sounds were somewhat distant, but normal. Peripheral pulses were present and normal throughout. Neurologic findings were within normal limits.

An intravenous aortogram was performed several hours after admission, utilizing 85 cc. 90 per cent diatrizoate sodium (Hypaque).* The x-ray films revealed a tortuous

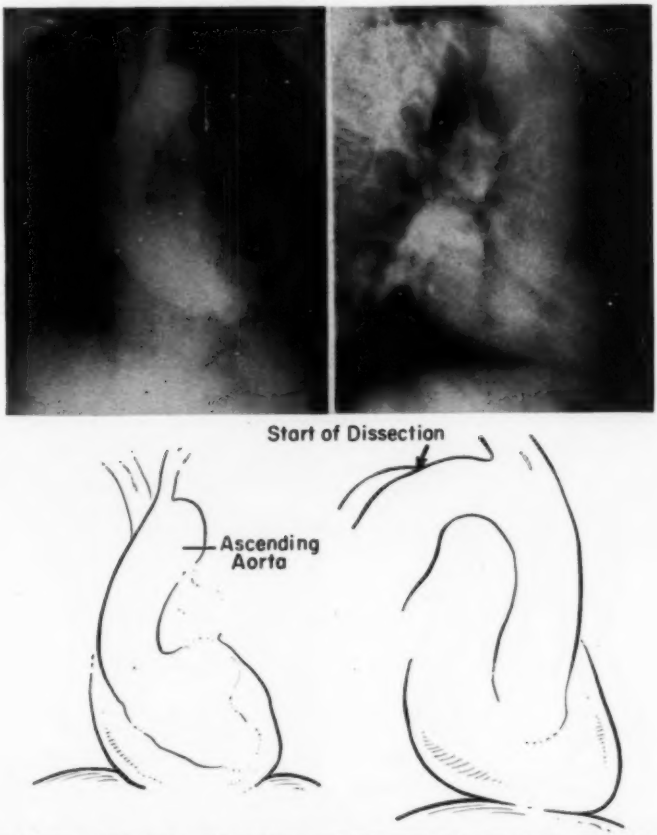

FIGURE 3 (Case 2): The left atrium and left ventricle are filled. The dissection is seen commencing distal to the origin of subclavian and projecting posteriorly.

*Generously supplied by Winthrop Laboratories, Inc.

aorta with a double aortic lumen originating just distal to the left subclavian artery take-off, and extending through the diaphragm (Figs. 1 and 2).

Thoracotomy was performed that afternoon through the bed of the fifth rib. A dissecting aneurysm was found in the predicted anatomic location. The maximum width of the descending aorta in the area of the aneurysm was 6 cm. in diameter, as compared to a diameter of 3.5 cm. just proximal to the origin of the dissection. The aorta was incised transversely between occluding clamps, just beyond the origin of the dissection and a re-entry procedure, as described by DeBakey,[3] was performed. Despite the gradual removal of the occlusive aortic clamps, a marked hypotensive episode ensued. This responded to partial reocclusion of the aorta and intracardiac adrenalin, following which the patient's condition stabilized. The thoracotomy was closed and he was transferred to the post-anesthesia recovery room. However, he failed to gain consciousness, and over a period of approximately three hours, sustained a gradual fall in blood pressure which failed to respond to intensive treatment.

Post-mortem examination revealed that the dissection had progressed proximally to include the entire ascending aorta and the origins of all the brachio-cephalic and coronary vessels. In addition, there was severe subepicardial extravasation arising from the root of the aorta.

Case 2, E.D.: This 65 year-old white woman was admitted to the University of Minnesota Hospitals on April 23, 1959. In December of 1958, she had experienced a sudden, severe tearing left hemithoracic pain which was primarily located in the back and extended around to the lower anterior chest wall. She was hospitalized elsewhere and a left pleural effusion with some underlying pneumonitis was noted. The possibility

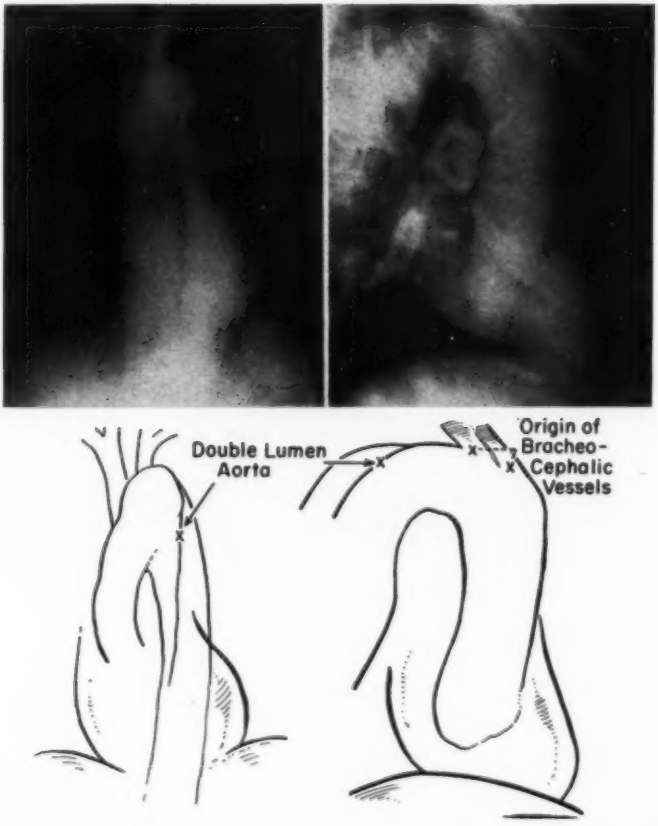

FIGURE 4 (Case 2): Later film—the large size of the dissection is better appreciated. Two channels can be seen on the AP film as well as on the lateral.

of a spontaneous perforation of the esophagus was entertained, but the patient's condition improved and no further studies were performed.

In the intervening five months, she had frequent recurrent bouts of severe left anterior chest pain. A chest x-ray film taken approximately two months after her initial episode showed some broadening of the mediastinal shadow.

The admission physical findings were essentially normal. All peripheral pulses were present and normal. Plain films of the chest revealed a broadening of the descending thoracic aorta beginning just distal to the aortic knob. An intravenous aortogram was performed utilizing 75 cc. of 90 per cent Hypaque. The x-ray films revealed a widening of the thoracic aorta which originated approximately 3 cm. distal to the origin of the left subclavian artery. This portion of the distal arch and the descending thoracic aorta contained two channels which appeared to extend almost to the level of the diaphragm (Figs. 3, 4, and 5).

At operation, a dissecting aneurysm of the thoracic aorta was found, originating approximately 3 cm. distal to the take-off of the left subclavian artery. The aorta appeared to approach normal diameter in the region of the diaphragmatic hiatus. The aorta measured approximately 4.5 cm. in diameter both proximal to the aneurysm and at the diaphragm. The maximum breadth of the aneurysm was 9 cm.

Extracorporeal bypass from the left atrium to the left femoral artery was instituted, the aorta was cross-clamped above and below the aneurysm, and the isolated descending segment opened. There was no significant back bleeding from the intercostal vessels in this area. This suggested that the aneurysmal dissection had disrupted the take-off of the intercostal vessels in this segment and that resection of this segment would not further diminish blood flow to the spinal cord. Accordingly, the entire descending thoracic aorta was excised and replaced with a woven dacron graft. The patient tolerated the procedure well and, except for a minimal amount of amnesia during the first postoperative day, had no neurologic deficit.

Case 3, H.J.: This 63 year-old white man was admitted to Minneapolis General Hospital on April 2, 1960, with a history of sudden severe diffuse chest pain which began two and one-half hours prior to admission and lasted for five minutes. It was followed by the development of paralysis from the hips down, and the onset of blanching and coolness of both legs. On admission, the temperature was 97, pulse 100, blood pressure 140/70. He was acutely ill with mottled, pale lower extremities. Carotid and radial pulses were palpable bilaterally. Femoral and popliteal pulses were absent bilaterally. He was unable to move either leg. The cranial nerves were intact. There was paralysis of both legs; both arms moved normally. Sensation was absent from a line 4 cm. below the umbilicus down. Deep tendon reflexes were absent in both legs and normal in both arms.

About an hour after admission, femoral, popliteal and posterior tibial pulses suddenly returned, bowel sounds became normal, and urine output occurred. In addition, the paleness and mottling of the lower half of the body disappeared. A tentative diagnosis of dissecting aortic aneurysm with re-entry into the abdominal aorta was made. He was treated conservatively and transferred to University Hospitals on May 9, 1960 for aortography.

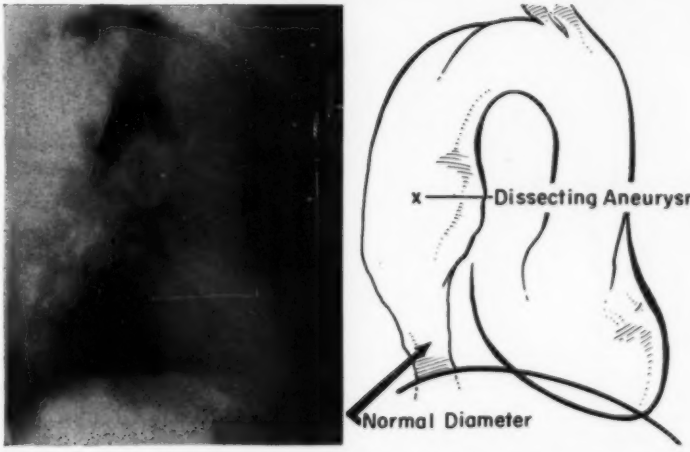

FIGURE 5 (Case 2): The aortic lumen narrows just above the diaphragm to a normal size indicating that the dissection is confined to the thoracic aorta.

An intravenous aortogram was performed utilizing 100 cc. Hypaque—90 per cent. An aneurysm was noted to originate just distal to the left subclavian artery. There was a filling defect of the lateral aspect of the descending thoracic aorta which occluded more of the aorta progressing distally to the diaphragm (Fig. 6). In the lateral view, the ascending aorta was well-visualized, and of normal diameter. The descending aorta was not opacified in any of the films, presumably because of its ribbon-like character.

He refused to consider surgical intervention, and was discharged from the hospital.

Case 4, J.McK.: This 47 year-old white man was admitted to Grace-New Haven Community Hospital on March 21, 1960. He had a 15-year history of hypertension. The evening prior to admission he experienced the sudden onset of left shoulder pain followed by numbness in the left arm. A physician examined him and noted absence of the left femoral pulse. He was admitted to a local hospital where a diagnosis of embolus of the left iliac artery and aorta was seen. This seemed to extend up to the level of the diaphragm. The incision was closed and he was transferred to the Yale-New Haven Medical Center.

On admission to this hospital, his blood pressure was 100/60, pulse 90, and respiration 16 per minute. He was in obvious acute distress and had considerable abdominal and back pain. The heart sounds were somewhat distant and the second aortic sound was increased. The lungs were clear.

An intravenous aortogram was performed using 85 cc. of 85 per cent renografin (Cardiografin).* The x-ray films showed the presence of a double lumen commencing just distal to the takeoff of the left subclavian artery. This double lumen appeared to extend down to and below the level of the diaphragm (Figs. 7 and 8).

He was immediately taken to the operating room where a DeBakey re-entry procedure was performed. The aorta was divided just distal to the left subclavian artery with closure of the distal dissection plane and partial closure of the proximal dissection allowing a window for re-entry into the aortic lumen. This was accomplished during partial aortic bypass (left auricle to femoral artery).

The postoperative course was uncomplicated and he has been discharged to full activity. Two and one-half months following surgery, all of his peripheral pulses were present and of good quality.

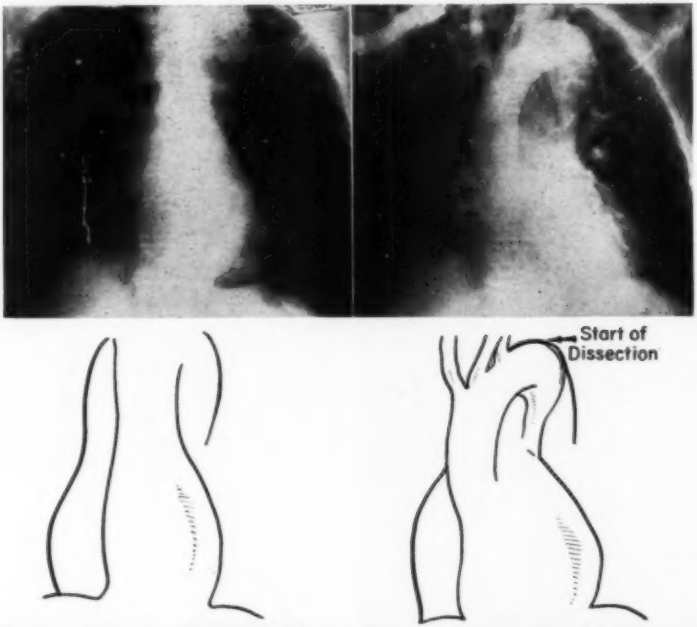

FIGURE 6 (Case 3): Left—preliminary film, no contrast material. The aorta is tortuous and dilated. Right—the ascending aorta is well visualized by Hypaque. There is a marked narrowing in the region of the descending aorta distal to the takeoff of the brachiocephalic vessels starting at the arch. This is the area of dissection partially filled with clot.

*Supplied by E. R. Squibb.

Case 5, C.G.: This 75 year-old white woman was admitted to Grace-New Haven Community Hospital on April 29, 1960 with a three-day history of severe and constant interscapular pain. Chest x-ray films showed elongation and widening of the aortic shadow and questionable left pleural effusion.

Blood pressure was 150/100, pulse 84, respirations 20. All pulses were present and active in extremities. Examination of the chest revealed no definite abnormality. Shortly after admission, an intravenous aortogram was done utilizing 75 cc. of 90 per cent Hypaque. A dissecting aneurysm with a double lumen shadow beginning immediately beyond the origin of the left subclavian artery was seen. Although the ascending aorta was generally dilated, there was no evidence for a dissection in this area. The dissection was felt to extend to the level of the diaphragm and possibly below.

She was taken to the operating room where a diagnosis of dissecting aneurysm was confirmed. The dissection began at the origin of the left subclavian and extended to the level of the diaphragm. Partial bypass of the left heart was instituted between the left auricle and the femoral artery. A partial resection of the dissecting aneurysm was accomplished with replacement by a Teflon graft.

Discussion

The emphasis of DeBakey[3] and Cooley[2] on a thoracic approach for the surgical treatment of dissecting aneurysms and their demonstration of the curability of these lesions, both by re-entry and resectional procedures, marked the first successful surgical treatment of this condition. DeBakey indicated that even in the acute situation, terminal rupture of the aneurysm into the pericardium, mediastinum, pleural or peritoneal cavity may be delayed for hours or even days, thus affording sufficient time for diagnosis and surgical treatment. In addition, there are a small number of subacute and chronic cases, some of which may have re-entered the aorta below their origin, which are amenable to surgical attack.

Dissecting aneurysms are rapidly fatal in 75 to 90 per cent of cases.[3] Therefore, it is imperative that an early nad accurate diagnosis be made, so that treatment may be initiated as rapidly as possible. The technique of intravenous aortography, as previously described,[1,4] permits a rapid definitive diagnosis with minimal risk to the patient. Admittedly, standard retrograde aortography results in more vivid aortic delineation. However, the risks involved outweigh the improvement in contrast. Standard forward angiocardiographic techniques may also be employed. However,

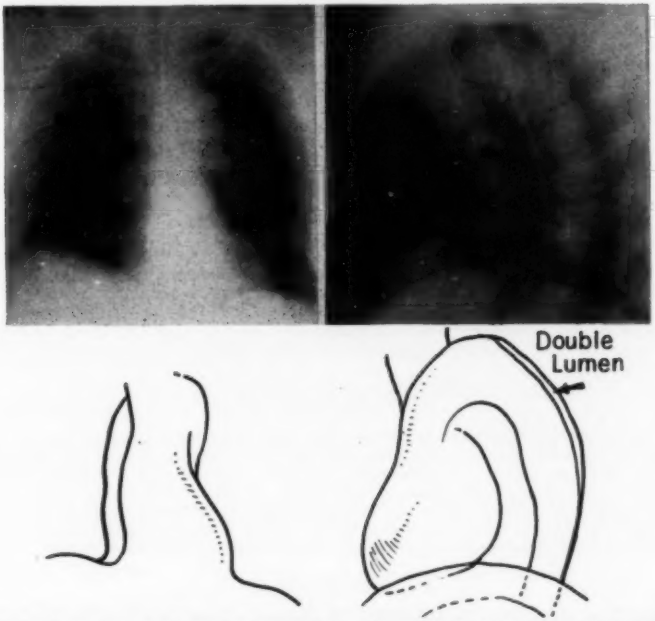

FIGURE 7 (Case 5): Left preliminary film—the aorta is tortuous and elongated. Its wall is slightly irregular. Right lateral film from intravenous aortogram. Double lumen is clearly shown posteriorly extending to level of diaphragm.

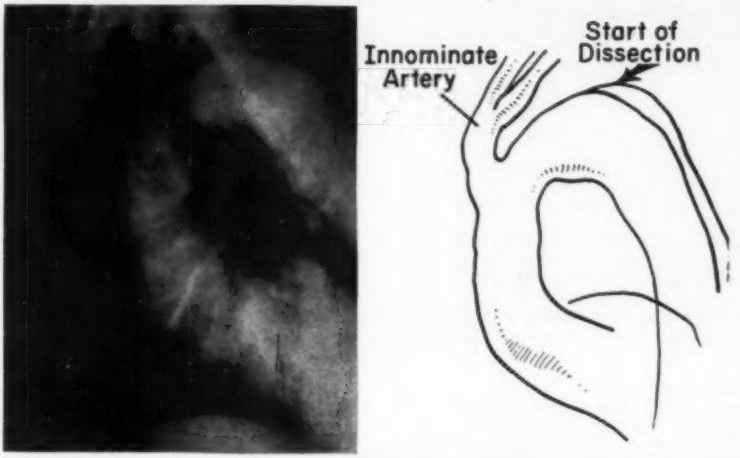

FIGURE 8 (Case 5): Steep LAO view from intravenous aortogram showing dissection commencing in the arch distal to the left subclavian artery. The double lumen is seen posterior to the main body of contrast in the aorta. The ascending aorta is dilated but there is no evidence for a double lumen or dissection in this region.

their diagnostic qualities may be further enhanced by the use of more radiopaque contrast material and more rapid injection.[1,8]

In general, we have employed doses of 1 to 1.3 cc. of Cardiografin-85® or Hypaque—90/kg. body weight. Serial films are started five seconds after the injection and are continued at a rate of two per second for approximately ten seconds.

Dissection commonly starts either as a transverse tear in the intima of the ascending aorta a few centimeters above the aortic valve, or as an intimal tear just distal to the origin of the left subclavian artery. In the former group, and in those in whom dissection originates distal to the brachiocephalic vessels, but extends retrograde to include the aortic arch, there appears to be little place for a resectional procedure at present. In these patients, a re-entry procedure performed in the descending thoracic aorta is the operation of choice.

On the other hand, upon the demonstration of a lesion which originates distal to the left subclavian artery and appears to be confined to the descending thoracic aorta, a resection should certainly be considered. If these findings are confirmed at thoracotomy, extracorporeal circulation from the left atrium to the femoral artery should be instituted,[2] the aorta clamped above and below the aneurysm, and the aneurysmal portion of the aorta opened.

Brisk back-bleeding from the intercostal vessels into the aneurysm would suggest that the dissecting process has not occluded the origin of these vessels. Under these circumstances, resection of the involved segment of thoracic aorta would deprive the spinal cord of blood from whatever tributaries to it arise from the resected segment, thus increasing the risk of ischemic cord damage.

It should be kept in mind that the radiologic studies may be non-diagnostic if the intimal tear has sealed and the dissection is filled with clot, or in cases in which there is no intimal tear.

SUMMARY

Patients who exhibit clinical evidence of a dissecting aneurysm of the aorta should be examined by a forward angiographic technique as rapidly as possible. It is felt that the use of large amounts of radiopaque contrast material and a mechanical injector will increase the diagnostic value of the films obtained. Upon the basis of precise anatomic knowledge of the origin and extent of the dissecting process, a well-conceived surgical plan of attack can be developed. Five cases which demonstrate this approach are presented and the method of surgical management is briefly discussed.

RESUMEN

Los pacientes quemuestran evidencias de un aneurisma disecante de la aorta deben ser examinados por medio de la técnica angiocardiográfica tan pronto como sea posible. Se cree que el uso de grandes cantidades de medio de contraste y de un inyector mecánico aumenta el valor diagnóstico de las películas obtenidas. Basándose

en el conocimiento anatómico preciso del origen del proceso disecante un plan bien concebido de tratamiento quirúrgico puede realizarse. Se presentan cinco casos que demuestran este proceder y se discute brevemente el tratamiento quirúrgico.

RESUMÉ

Les malades pour qui on peut faire la preuve clinique d'un anévrysme disséquant de l'aorte devraient être examinés aussi tôt que possible, par un procéde angiographique rapide. L'auteur pense que l'emploi de grandes quantités de milieu de contraste radio-opaque et un injecteur mécanique augmentera la valeur diagnostique des films obtenus. Sur la base d'une connaissance anatomique précise de l'origine et de l'étendue du processus disséquant un plan d'attaque chirurgical bien conçu peut être développé. Cinq cas qui démontrent cette tentative sont présentés, et la méthode de traitement chirurgical est brièvement discutée.

ZUSAMMENFASSUNG

Patienten, die klinisch Anhaltspunkte für ein Aneürisma dissecans der Aorta bieten, müssen so schnell wie möglich durch eine angiografische Technik untersucht werden. Es wird die Überzeugung ausgeesprochen, daß der Gebrauch großer Mengen von strahlendichten Kontrastmitteln und ein mechanischer Injektor den diagnostischen Wert der gewonnenen Röntgenfilme verbessern. Es kann auf der Basis einer Präzisen anatomischen Kenntnis des Ursprunges und des Ausmaßes des ablösenden Prozesses ein wohl abgewogenes chirurgisches Vorgehen ausgearbeitet werden. Kurze Besprechung von 5 Fällen, die diesen Weg demonstrieren, werden vorgestellt und die Methode ihrer chirurgischen Behandlung besprochen.

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SUMMARY OF CURRENT THERAPY

Edited by Eliot Corday, M.D.

Dosage Schedules in Anticoagulant Therapy

The anticoagulant agents represent the greatest and most helpful advance in cardiovascular therapeutics in the past 20 years. No longer does the question of usage of the agents arise—the only questions to be answered are:

(1) when should anticoagulants be used?

(2) how should the anticoagulants be used?

I. When to Use Anticoagulants

Until safer and more effective agents are found to prevent crippling thromboses with their associated cerebral, pulmonary, cardiac, hepatic, renal, splenic and extremity infarctions, anticoagulants should be used in all patients in whom thromboembolic phenomena have occurred or are likely to occur.

The contraindications to their use include blood dyscrasias, ulcerative lesions of the gastrointestinal tract, a serious and uncontrollable degree of arterial or pulmonary hypertension, serious liver or kidney disease, an unreliable laboratory for control studies and most of all an uncooperative and unreliable patient.

II. How to Use Anticoagulants

(a) the physician should continue to use the anticoagulant with which he is most familiar.

(b) a reliable laboratory with a battery of trained technicians who can do accurate Lee-White and prothrombin times.

(c) the physician should choose an orally-active anticoagulant agent with the knowledge that all known agents available today are equally effective agents when properly administered.

(d) time and the urgency of the thromboembolic state should determine the choice of the anticoagulant.

Aqueous sodium heparin should be the emergency anticoagulant. Aqueous sodium heparin is available from many pharmaceutical manufacturers in a wide variety of concentrations; for example, 1,000 units (10 mg. per cc.), 5,000 units (50 mg. per cc.), 10,000 units (100 mg. per cc.), 20,000 units (200 mg. per cc.) and 40,000 units (400 mg. per cc.) are available in rubber sealed vials of 1 to 10 cc. for multiple dose injections or in plastic single dose injectables.

Heparin

Heparin is administered intravenously for immediate anticoagulant effect. The dose is selected according to the patient's size.

In a grave emergency, such as a severe and prolonged attack of angina pectoris, heparin is given without waiting for a Lee-White coagulation time.

Intravenous heparin may be continued every four hours in a dosage of one-half the initial dose to keep the Lee-White coagulation time at or near two to three times the patient's normal until such time as the orally administered anticoagulant becomes effective. It is preferable to use the subcutaneous method which will maintain the 11th hour Lee-White coagulation time at or near twice the normal. Lee-White coagulation time is determined each morning at 8 a.m. and the following procedure is adhered to rigidly:

(1) drug—concentrated heparin, either 200 mg. or 400 mg., that is, 20,000 or 40,000 units per cc. strength of aqueous heparin.

(2) dosage—100 mg. concentrated heparin for patients under 140 pounds, 125 mg. for patients 140 to 160 pounds and 150 mg. for patients above 160 pounds.

(3) time—every 12 hours, preferably 9 a.m. and 9 p.m.

(4) Site of injection—deposit under the skin into the fat overlying the iliac crest or the anterior abdominal wall.

(5) the heparin should be measured out in a tuberculin syringe and a one-half inch 26 gauge needle used. The skin should not be rubbed before or after the injection, and should not be pinched. The tip of the needle should not be moved. The heparin is deposited under the skin and light pressure made over the puncture site.

In a recently published study it was clearly demonstrated that concentrated heparin used in the above manner was the preferable and feasible drug in a large county understaffed hospital. The maintenance of anticoagulation was well maintained, with few dips below the desired level, resulting in a lowered mortality rate, fewer thromboembolic episodes and less serious bleeding than in a comparable series treated at the same time and by the same personnel using an oral anticoagulant bishydroxycoumarin (Dicumarol).

Subcutaneous concentrated heparin has been used in a large series of physician patients who had suffered one or more occlusions of the coronary, cerebral or peripheral arteries. Subcutaneous heparin was administered in the aforementioned manner, except that a single dose was administered by the physician himself each evening at or near 9 p.m. No control of the Lee-White level was found necessary since no bleeding occurred in this group. In 1,860 patient-months of treatment in this manner, only two of the patients had a recurrence of thrombotic episodes and there was no serious complication from the drug requiring either temporary withdrawal or cessation of the heparin therapy.

Oral Anticoagulants

Oral anticoagulants are administered when thromboembolic phenomena are threatened or have occurred in a patient in whom such contraindications as blood dyscrasias, bleeding gastro-intestinal or renal lesions and serious hepatitis, are not found.

The physician should treat his patient with the oral anticoagulant with which he is familiar and use a laboratory in which he has confidence.

The primary anticoagulant dosage is usually four times the maintenance dosage; for example, if Dicumarol is used and the initial base line prothrombin time is 100 per cent of control values or greater, 300 mg. should be administered; when the prothrombin time is 80 to 100 per cent of control, then 200 mg., between 60 and 80 per cent of control, then 100 to 200 mg., and if below 60 per cent, heparin should be used until such time as a determination of the liver function is accomplished.

The prothrombin time should be prolonged to the desired level of 25 to 30 seconds; *i.e.*, from 15 to 25 per cent of control, and maintained at or near this level until the danger of thromboembolic phenomena has passed and the patient is active physically.

An oral anticoagulant should never be administered without an adequate laboratory, preferably one which performs the test frequently and preferably which uses the Quick or the P and P method.

The physician must be careful to make very little change in the daily anticoagulant dosage once the desired prothrombin level has been reached. An ideal way of dosage management is somewhat as follows: after the desired prothrombin level has been attained, add the total amount of coumarin drug utilized per week and divide this dosage by 7. This should then give the required daily dosage which should prove adequate for an indefinite period unless liver disease, gastroenteritis or a laboratory error should cause the prothrombin time to change markedly. The following schedule is easily followed by the physician in prescribing the daily dosage of the anticoagulant. Dicumarol is used only because it is the oldest and most widely used anticoagulant drug.

Schedule to achieve an effective anticoagulation level of 25 to 30 seconds or 20 to 25 per cent of control may be as follows:

Prothrombin Time		Dicumarol Dose
100 per cent of control or above	=	300 mg.
80 to 100 per cent of control	=	200 mg.
60 to 80 per cent of control	=	150 mg.
40 to 60 per cent of control	=	100 mg.

A daily maintenance dosage usually proves to be one-seventh of the total anticoagulation dosage.

In arterial occlusive disease of the extracranial and cerebral arteries, coronary arteries, or the peripheral arteries and veins the anticoagulation drug should be continued as long as there is a threat of recurrence of the thromboembolism.

Heparin or oral anticoagulant dosage should be gradually reduced and not be withdrawn abruptly because of the danger of the prompt occurrence of thromboembolism in vessels in which the disease has not been manifest, but hidden because of the anticoagulant state.

In dental extractions the prothrombin level may be allowed to rise to 40 to 45 per cent of control levels. If there is any post-extraction bleeding, it is readily controlled by an intravenous dose of 10 to 20 mg. of conjugated estrogen substance. This dosage may be repeated in two or three hours, if necessary, without danger of depressing the prothrombin time

or increasing the per cent of time control above the 40 to 45 per cent level. In cardiovascular surgery, most operations are successfully performed with the prothrombin level at or near 45 per cent of control values. In prostatic surgery, especially transurethral resection, the prothrombin time should be near the normal of 100 per cent because of the difficulty in hemostasis in the markedly congested prostatic area. Rarely is it necessary to use vitamin K oxide and this agent should not be used unless absolutely necessary because of the rebound phenomenon.

Finally, it is believed that until fibrinolytic therapy is readily available and practical the physician should continue to use the anticoagulant drug of his choice in every patient whose morbidity and mortality are jeopardized by thromboembolic phenomena.

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VECTORCARDIOGRAM IN POSTERIOR MYOCARDIAL INFARCTION

The vectorcardiograms of 25 patients with dorsal infarction of the heart were studied. These infarctions were classified into four groups as follows, all of which showed an increase of the R wave in the B (anterior-posterior) component of Grishman's cube system: (1) strictly dorsal infarction, showing only an increase of the R wave in the B component. In this group were three cases, including one complicated by complete right bundle branch block; (2) inferodorsal infarction, showing pathologic Q waves in the C (superior-inferior) component. There were five cases in this class; (3) laterodorsal infarction, showing abnormal Q waves in the A (right-left) component. Eight cases were placed in this class; (4) inferolaterodorsal infarction, with abnormal Q waves in the A and C components. There were nine cases, including two complication by complete right bundle branch block, in this group.

The vectorcardiograms of these cases showed increased magnitude and forward orientation of the initial portions (0.02 second) of the ventricular activation loop. These initial portions frequently had a higher speed of inscription due to the absence of opposing forces. The necrotic areas in the dorsal wall which should undergo early depolarization were not activated at the same time; therefore, no electrical forces were produced in those areas.

In dorsal infarction, the rotation of the QRSsE in the horizontal plane was predominantly counterclockwise. This, together with the direction of predominant forces forward (average 0.048 second) and the orientation of the TsE in the same direction, facilitates the diagnosis of dorsal infarction in these cases in which a tall R wave in the right precordial leads might suggest right ventricular hypertrophy. In all cases, a certain delay of inscription and deformity in the morphology of the terminal portions of the QRS loop was observed. This delay was explained by a possible conduction disturbance during late activation of still depolarizable muscular masses in the infarcted area.

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ELECTROCARDIOGRAM OF THE MONTH

Edited by Stephen R. Elek, M.D.

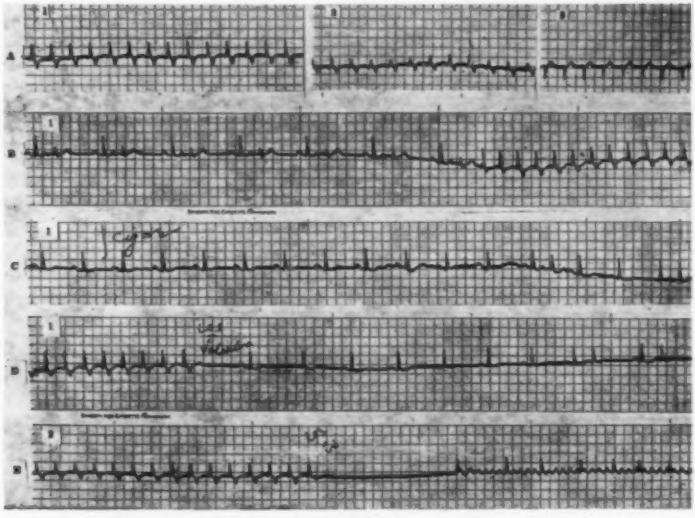
Pseudo-Nodal Rhythm Caused by Cigar Smoking

A 55 year-old male was admitted to the Philadelphia General Hospital for pain in the left chest and back, ankle edema, and rapid heart action. The past history revealed that he had been refused life insurance three years previously because of a rapid rhythm. Peculiarly, he had noted frequent episodes of fluttering of the heart during the past ten years, usually caused by cigar smoking. On admission, the blood pressure was 160/106 mm.Hg. Several electrocardiographic strips are presented to illustrate disturbances of impulse formation in the atria.

1. *Strip A:* A rapid rhythm is present at 148/min. The P waves are inverted in limb leads 1 and 2 and upright in limb lead 3. The inverted P waves appear to follow the QRS suggesting retrograde inscription from a "lower nodal" pacemaker. An alternative explanation would suggest "upper nodal" rhythm with a relatively long conduction time below the A-V node (first degree A-V block) with no delay in conduction retrograde to the atria. However, both explanations are untenable as can be proven in the subsequent tracings.

2. *Strip B:* A sinus rhythm is present with a P-R interval of 0.20 sec. Frequent premature P waves are seen with the P-R interval lengthening to 0.24 sec.

Attention is called to the bizarre contour of the first beat of the tachycardia which shows a smaller R wave with a deep slurred S wave. This beat terminates a short cycle length which followed upon a long cycle length and demonstrates aberrant ventricular conduction. This illustrates the dependence of the ventricular refractory period on the cycle length.



Furthermore, prolongation of the P-R interval, as well as the aberrent ventricular conduction, are due to the occurrence of the premature atrial systoles early in the ventricular cycle, so that they reach the A-V junction and the ventricles in their relative refractory phase. The second beat of the run of tachycardia has a P-R interval of 0.26 seconds, the third beat 0.30 seconds, and finally the P-R interval lengthens to 0.36 seconds during the extended run of the tachycardia. The contour of the P waves gradually change until they are entirely inverted.

Several alternative explanations must be considered:

(1) The development of coronary sinus rhythm: This is not the case as the P-R interval is quite prolonged (Scherf did not consider any cases with a P-R interval greater than 0.17 sec.). Furthermore, the P waves are inverted in limb leads 1 and 2, rather than in limb leads 2 and 3.

(2) Upper nodal rhythm in the presence of first degree forward A-V block is ruled out by a normal P-R of the sinus beats.

(3) Two objections exclude lower nodal rhythm:

(a) the P waves are inverted in limb leads 1 and 2, rather than in limb leads 2 and 3.

(b) the ectopic beats are definitely atrial in origin and the P configuration in the runs of tachycardia merely suggest a wandering of the pacemaker to a region of the atria near the A-V node.

(4) An altered position of the heart is excluded since the P waves are upright in the sinus beats of limb leads 1 and 2.

3. *Strip C:* Demonstrates the onset of premature atrial systoles followed by a run of tachycardia. This particular episode was engendered by smoking a cigar. This association was confirmed on numerous occasions

4. *Strip D:* Shows the termination of the arrhythmia by left carotid sinus pressure and the valsalva maneuvre. In this instance a retrograde P wave is seen which is not followed by a QRS complex. This was considered as evidence of second degree A-V heart block in a forward direction. Sinus rhythm was re-established with occasional premature atrial systoles as seen in the right hand portion of the strip.

5. *Strip E:* The termination of the arrhythmia was accompanied again by left carotid sinus pressure and the valsalva maneuvre. On this occasion the tachycardia merely terminated and was followed by sinus arrest due to suppression of all pacemakers by the ectopic rhythm. Finally, a sinus beat "escaped" but is followed by impure atrial flutter (380/min.). The exhibition of atrial flutter implies an atrial rather than a nodal origin of the ectopic rhythm.

A sinus rhythm was re-established following digitalization without subsequent episodes of rapid heart action. This case illustrates the problem in differentiating paroxysmal nodal tachycardia from ectopic atrial rhythm with delayed A-V conduction. The term "pseudonodal" rhythm is used to alert the electrocardiographer to the pitfalls of a simple interpretation of nodal rhythm in the presence of inverted P waves in several of the standard limb leads.

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Philadelphia, Pennsylvania

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**Senior Resident in Medicine, Philadelphia General Hospital.

Critical Evaluation of a Recent Trial of Isoniazid Prophylaxis*

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Washington, D. C.

A paper entitled "The Immediate Effectiveness of Isoniazid Chemoprophylaxis as Determined by the Tuberculin Test," by Drs. Dahlstrom, Wilson and Sedlacek, appeared in the December, 1960, issue of *Diseases of the Chest*.[1] The final paragraph reads as follows: "No conclusion is justified until the biostatistical analysis of the data is completed. However, it may be inferred now that: (1) It is safe to administrate INH to children in the dosage used daily for as long as two years. (2) INH will greatly increase the rate of reversion of the tuberculin reaction to negative. (3) INH is not particularly effective in protecting a large and scattered population of children against tuberculous infection. (4) The ultimate effect upon immunity and resistance to tuberculous disease is still to be determined."

The validity of inferences (2) and (3) are open to serious question on several points. First, there are marked discrepancies in various counts of the study population in the paper. Second, the design of the study would not be likely to accomplish its major purpose, namely, to provide a control group whose experience could be utilized as a "base-line" for the treated group. In fact, there is evidence that it did fail in this respect. And finally the findings themselves not only illustrate the inadequacy of the control group but are so paradoxical as to cast doubt on their credibility.

Discrepancies in Accounting

In their text, the authors state that 1201 children were lost from the program in the first year. Since 5,555 children were included initially, this number of withdrawals would leave 4,354 for retesting at the end of the year. However, in the tables on conversions and reversions, it is stated that 4,530 initially negative reactors and 572 positive reactors were retested at that time. Even if none of the 162 doubtful reactors was retested, these tables indicate 5,102 children were present at the end of the year, or 748 more than stated in the text.

As a further illustration of accounting problems, an earlier report of this study[2] shows the number of subjects in Group I—those "first tested in 1955"—to be 1,988. The present report shows 2,826 with no explanation for the additional 838 children in Group I. Major discrepancies like these raise serious doubts about the validity of the entire analysis.

Deficiencies of the Study Design

The purpose of a controlled trial is to study two groups of subjects who are similar in all important respects except for the treatment being

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investigated. Since the likelihood of achieving this purpose depends on the design and execution of the trial, authors should describe the pertinent features of the procedures they employed.

The paper states that the treated and untreated groups were selected by pairing "villages" (except for the large Zuni reservation) by population and tuberculin sensitivity, a coin being tossed to determine which village of each pair was to receive INH. There were apparently 15 or 17 "village" pairs (15 in the 1960 report, 17 in the 1957 report) with a tremendous variation both in population and in prevalence of tuberculin reactors. According to the 1957 report,[3] the smallest village had 22 children and the largest 320. Some villages had no tuberculin reactors while the highest reactor rate was 48 per cent. With such extreme ranges, the method used to assign treatment could easily produce groups which were initially dissimilar.

Furthermore, there is no assurance that the two groups were handled similarly throughout the period of observation. Indeed, the study design makes it questionable that this trial was "doubly-blind." Although placebo and isoniazid tablets were said to be similar in size and shape, they must have been markedly dissimilar in taste since the placebo was "simply a tablet of lactose." Except for the large group of Zuni Indians, it is probably true that most study participants did not have a chance to compare tablets because the same medication was assigned to an entire village. But the serious danger inherent in this situation is that the identification of a single tablet would reveal the product for an entire village. Once the product is known the results for that village can no longer be assumed to be unbiased.

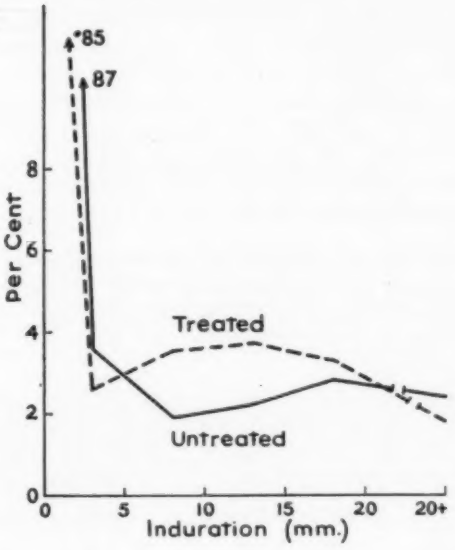

FIGURE 1: Distribution of Indian children in treated and untreated groups by size of reaction to 5 T. U. of PPD-S.

Dissimilarity of Untreated and Treated Groups

Very little information about the initial characteristics of the two groups is given in this report. Only 3 criteria are mentioned by which the success of the allocation procedures in producing two initially similar groups can be judged. The total number of subjects tested in each group (2,687 and 2,577) is probably as close as one could expect with the small number of villages to be paired. The authors state that "the treated and control groups were comparable as to age distribution and tuberculin reactions (see Chart A and Table 1)." No further information about age is given (Chart A is missing) but the two groups are definitely *not* similar with respect to tuberculin sensitivity. This is clearly shown in the accompanying figure. Of the group on isoniazid, 7.2 per cent had reactions in the 6 to 15 mm. range compared with 4.2 per cent for the untreated group. A Chi-square test of the two distributions shows that the difference between them is highly significant.

Some pertinent and available information is omitted. For instance, the prevalence of tuberculosis revealed by the initial x-rays would be helpful in assessing the previous tuberculosis experience of the two groups. And in a study of tuberculin sensitivity, it is surprising that the proportion of children previously vaccinated with BCG is not stated.

Credibility of the Reported Findings

The authors' principal findings may be summarized by stating that isoniazid on the one hand was quite effective in causing tuberculin reversions while on the other it did little to prevent new tuberculous infections. A little reflection reveals the paradox inherent in these two conclusions. In the first place, one year would seem to be a remarkably short time for specific tuberculin sensitivity to disappear even with the possible help of isoniazid. But in marked contrast to this favorable effect among children who were already reactors and who must, for the most part, have had quiescent infections, isoniazid was said to have afforded only feeble protection against new infections in which the invading organisms could hardly have escaped considerable exposure to the drug.

Another unexplained paradox is the marked difference in conversions and reversions among the treated subjects in Groups I and II. This is shown in Table 1, constructed from the published data. (Similar data for the untreated subjects were not given).

TABLE 1—REPORTED CONVERSION AND REVERSION RATES AMONG TWO SEGMENTS OF THE GROUP OF CHILDREN WITH ISONIAZID FOR 1 YEAR, BY INITIAL TUBERCULIN STATUS

	Initially Negative Children			Initially Positive Children		
		Conversions			Reversions	
	Total	Number	Per cent	Total	Number	Per cent
Group I	1189	8	0.7	178	45	25.3
Group II	1002	33	3.3	142	3	2.1
Total	2191	41	1.9	320	48	15.0

When the authors' findings are put together in this manner, it is clearly evident that the effectiveness of isoniazid appears to be markedly different for the two groups, since there were few conversions and many reversions in Group I, and completely opposite findings in Group II. Since both groups received isoniazid, something else must have had a profound influence on the risk of conversions and reversions in this population. But if the results *within* the treated group can be so dissimilar—presumably as the result of some basic variation in population characteristics—it must be admitted that population differences might have accounted for the dissimilar experiences of the treated and untreated subjects.

One known difference between the treated and untreated subjects is the varying degree of tuberculin sensitivity. While the authors do point out that "most reversions to negativity were from levels of allergy producing reactions from 6 to 10 mm. in diameter," the potential significance of this observation is more clearly illustrated in Table 2, which is also constructed from the published data.

It can be seen that the reversion rate is much greater among persons with small "positive" reactions than among those with larger reactions. Since the treated group contained considerably more persons with small reactions than the untreated group, it is again clear that other population characteristics could account for much, if not all, of the differences ascribed by the authors to isoniazid.

TABLE 2—TUBERCULIN REVERSIONS AMONG TUBERCULIN REACTORS BY SIZE OF INITIAL REACTION

Initial Reaction Size	Initial Number	Reversions	
		Number	Per cent
6-10 mm.	142	32*	21.8
Over 10 mm.	430	26	6.0
Total	572	57	10.0

*This number might be 32—the text and tables disagree on the total number of reversions among the untreated group.

CONCLUSION

Although some very interesting questions might have been raised—and answered—by this study, further analysis or speculation is not warranted. The reported findings show major discrepancies, important information is omitted, and the design of the study gives no assurance that the untreated group can in any sense be considered a control for the treated group. Because of these deficiencies, the conclusions in this paper regarding the effect of isoniazid chemoprophylaxis on tuberculin sensitivity can not be accepted.

REFERENCES

1 Dahlstrom, A. W., Wilson, J. L., and Sedlacek, B. B.: "The Immediate Effectiveness of Isoniazid Chemoprophylaxis as Determined by the Tuberculin Test," *Dis. Chest*, 38:599, 1960.

2 Dahlstrom, A. W.: "New Mexico Field Tuberculosis Study Program," *Dis. Chest*, 31:113, 1957.

EDITORIAL NOTE

(Dahlstrom, A. W., Wilson, J. L., and Sedlacek, B. B.: "The Immediate Effectiveness of Chemoprophylaxis as Determined by the Tuberculin Test," *Dis. Chest*, 38:599, 1960.)

A project was proposed by the Committee on Indian Affairs of the American College of Chest Physicians to conduct a survey among Indian children in New Mexico as to the possibility of the use of INH as a prophylactic measure relative to tuberculosis. The Board of Regents of the College recommended that this proposal be presented to the Division of Indian Health of the U. S. Public Health Service. Dr. Arthur W. Dahlstrom, Chairman of the Committee on Indian Affairs, was authorized to discuss this matter with the Division of Indian Health of the Public Health Service and after considerable negotiations, Dr. Dahlstrom informed the Committee on Indian Affairs and the Board of Regents that the U. S. Public Health Service was willing to finance this study.

At a meeting arranged by the Division of Indian Health of the U. S. Public Health Service held in Washington, D. C., it was agreed that the study be undertaken by the Phipps Institute of Philadelphia, under the supervision of Dr. Julius L. Wilson. A contract was made with the Phipps Institute by the Public Health Service for this study. It was further agreed that any report from this study be submitted to *Diseases of the Chest*, the official journal of the American College of Chest Physicians, for publication. The American College of Chest Physicians assumed no responsibility for the mechanics of this research project and its only role was to publish the report, as submitted. We wish to point out the report was published in the December, 1960 issue of *Diseases of the Chest*.

Editor

MINERALIZING ELASTOSIS IN BLOOD VESSELS

The main histologic alteration in the blood vessels of tuberculous and bronchiectatic lungs reported in this paper consists of the degeneration of elastic fibers which appeared deeply basophilic in the hematoxylin and eosin stained sections. This particular change has been observed in some of the specimens only and not in all the lungs routinely examined. Special staining revealed that the basophilic nature of these fibres is due mainly to their encrustation with salts of calcium, stainable by von Kossa method. Occasionally, iron salts are also absorbed as shown by the Gomori iron reaction. The pathologic change in blood vessels has been called mineralizing elastosis, a phenomenon mostly manifest in the large or the medium sized intrapulmonary vessels. This change is sometimes associated with other accompanying abnormalities such as inflammatory cellular reaction in the vessel wall, medial disruption, intimal proliferative changes and giant cell response. The giant cells are observed in those instances where the elastic fibres not only show deposition of mineral salts, but are also fragmented. What is the nature of this disturbance is not clear. Why the lesions are confined mainly to the larger vessels also remains uncertain. A review of literature shows that identical changes in blood vessels of tuberculous and bronchiectatic lungs have not been described before.

Mention may also be made here of a few other lung conditions where a prominent histologic finding is degenerative change in the elastic fibres and their encrustation with minerals. In all these states, wherever there is fragmentation of the elastic tissue, there is an associated foreign body giant cell reaction. In man, the conditions which may be mentioned are idiopathic pulmonary hemosiderosis, pulmonary hemosiderosis of cardaic origin and pulmonary fibrosis and giant cell reaction with altered elastic tissue.

Gupta, I. M.: "Mineralizing Elastosis in Blood Vessels of Tuberculous and Bronchiectatic Lungs—A Preliminary Report on an Unusual Histological Change," *Indian J. Chest Dis.*, 3:1, 1961.

Editorial

The Necessity for Prompt, Accurate Diagnosis of Pulmonary Lesions

The numerous, enthusiastic, and frequently premature reports of the surgical treatment of bronchogenic carcinoma in the past two decades have all but disappeared from the medical literature. The unimproved resectability rate over a 25-year period and an overall operative mortality equal to that of the total five-year survival rate as reported from large medical centers, as well as the discovery of early blood stream invasion in this tumor, have had a discouraging effect on those dealing with this problem. Nitrogen mustard, used in conjunction with excisional surgery in patients having localized and completely resectable lesions, does not appear to materially reduce the progression of this early hematogenous disseminating cancer. An air of pessimism has spread to the point of resignation, and palliative irradiation and chemotherapy are advocated by many as the choice primary treatment of all bronchogenic carcinomas, even when resectable by present standards.

In an established thoracic surgical practice, the most gratifying moments are experienced with the annual return of patients having had resections of pulmonary malignancies years previously, who are leading a normal life. The agonizing finality for a particular patient with a lesion which has become nonresectable while under medical observation is a responsibility which we must accept. Excision of an early, and still local bronchogenic carcinoma has a high survival rate. The early diagnosis of bronchogenic carcinoma usually presents no problem; symptoms are not late, and roentgenograms of the chest, now universally available, will demonstrate changes in the film suggestive of carcinoma. Cytologic examination of bronchial secretions, bronchography as well as endoscopy can confirm the diagnosis. The difficulty does not lie at this point. The neglect occurs in our unwillingness to investigate symptoms and x-ray changes occurring early in bronchogenic carcinoma. A persistent cough and hemoptysis in a patient past middle age certainly should alert us to the presence of a carcinoma, and a few simple diagnostic procedures will either establish the diagnosis of bronchogenic carcinoma or indicate the presence of some other disease responsible for these symptoms. When in doubt, an exploratory thoracotomy can be resorted to with relative safety.

There has been reluctance on the part of physicians in general to accept surgical procedure for the establishment of an accurate tissue diagnosis, not only in carcinoma of the lung, but also in various other pulmonary diseases which present problems in diagnosis. A cervical lymph node biopsy will frequently be rewarding in mediastinal lymphadenopathy in Boeck's sarcoid, tuberculosis, or lymphoma nad will indicate nonresectability in carcinoma of the lung, however, is of no value in the diagnosis of most solitary tumors found within the mediastinum and lung. Pleural effusions may not present problems in diagnosis fol-

lowing removal and adequate study of the fluid; however, the pathologists still have occasional difficulty in differentiating inflammatory mesothelial reaction from malignant effusions. Needle biopsy of the diffusely involved pleura in tuberculosis and other infections may be helpful; however, in multiple small metastatic nodules such a biopsy may reveal normal pleura, unless by chance one of the scattered metastatic nodules is aspirated. Direct approach by utilizing a small thoracotomy and excision of a small portion of the pleura following visual and digital exploration will give an accurate diagnosis in most cases. Single solitary lesions of the lung, particularly when not associated with calcification, have now been accepted as indication for thoracotomy and excision. Prolonged, interval x-ray observations of such lesions in the adult may deprive a patient of a cure from a small bronchogenic carcinoma. Diffuse pulmonary lesions are frequently diagnosed without difficulty on the basis of occupational history, specific clinical and laboratory findings. However, in controversial cases, a small thoracotomy performed for the purpose of pulmonary biopsy is well tolerated even by patients who have low respiratory function. The accuracy of a diagnosis by microscopic, bacterial, and chemical analysis in such difficult cases cannot be denied.

Solitary tumors of the mediastinum, representing benign or malignant lesions, must be removed on x-ray discovery, particularly when not associated with peripheral lymphadenopathy. Cervical lymph node biopsy may indicate metastasis, and thoracotomy becomes unnecessary. However, when such lymph node biopsy is negative, thoracotomy for solitary, as well as multiple mediastinal tumors, should be performed for removal or biopsy purpose. Radiation as a diagnostic method in undiagnosed lesions should be relegated to antiquated medical practice.

We are living in a scientific medical age, and accurate diagnosis and specific therapy of most intrathoracic lesions are now possible. Our duty as physicians lies with our patients, and procrastination and empirical treatment of an undiagnosed intrathoracic lesion may constitute negligence.

KARL P. KLASSEN, M.D., F.C.C.P.
Columbus, Ohio

ERRATUM

The article "Tersavid (RO 4-1634), An Amine Oxidase Inhibitor, for the Treatment of Angina Pectoris" by Sydney J. Weisman, M.D., and Samuel A. Weisman, M.D., which appeared in the April, 1961 issue of *Diseases of the Chest*, was inadvertently published under the heading of Summary of Current Therapy.

REPORT OF THE WHITE HOUSE CONFERENCE ON CHILDREN AND YOUTH

The White House Conference on Children and Youth was held in Washington, D.C., March 27 to April 2, 1960. This conference, attended by over 7,000 delegates, was dedicated to the betterment of the lives of children and adolescents throughout the United States.

A great many recommendations were passed upon for inclusion in the final report and the following, a number of which were introduced by your delegate, were approved:

1. The inclusion of the tuberculin test as a yearly routine for all children. This routine is to be demanded of all school children similar to the routine of diphtheria, tetanus, pertussis, small-pox and poliomyelitis.
2. Further research on problems of congenital anomalies in children, which include anomalies relating to the respiratory tract such as tracheo-esophageal fistulas, agenesis of the lung, etc.
3. Further research on the increasing rate of infant mortality. This would include studies in causes and treatment of pulmonary hyaline membrane, congenital atelectasis, spontaneous pneumothorax of the newborn, and hypoxia of the newborn.
4. It was recommended that all school personnel including administrators, teachers, food-handlers, and custodians be required to have a yearly tuberculin test (if negative) and/or chest x-ray.

A number of other subjects discussed from all angles are at times indirectly related to respiratory problems. They included the conference discussions on mental retardation and cerebral palsy.

MILTON I. LEVINE, M.D., New York City
Official College Representative to the White House Conference on Children and Youth

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BOOK REVIEW

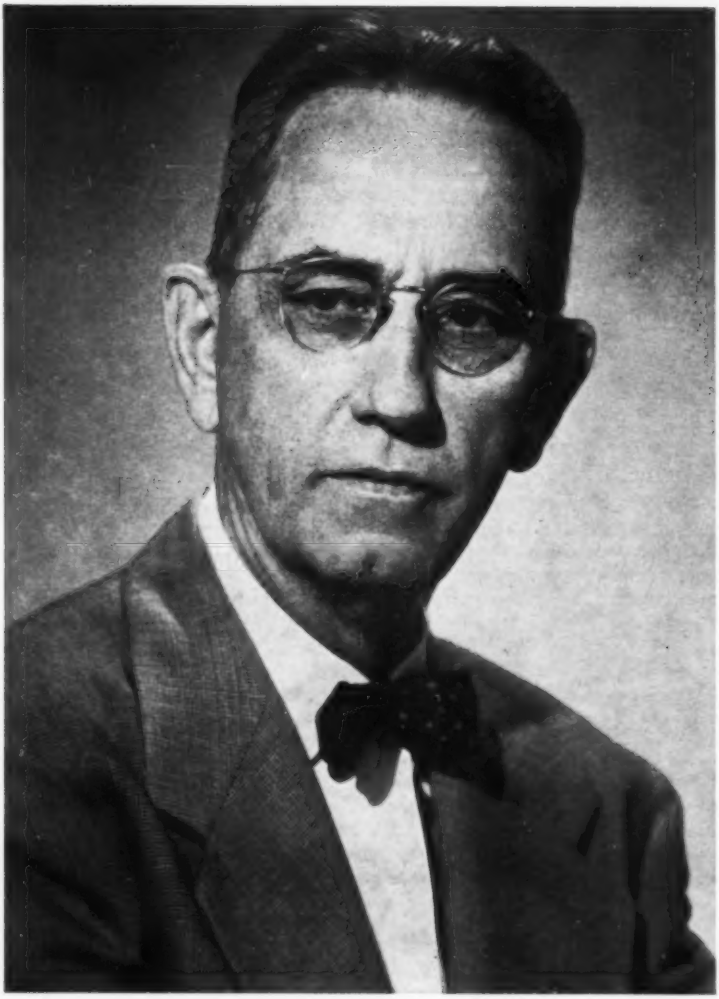
Gordon, Burgess L.: *Clinical Cardiopulmonary Physiology*, Ed. 2, New York, Grune & Stratton, Inc., 1960, 1001 pages, 728 illustrations. Price, $28.50.

The first edition of this text was a commendable experiment in compiling the many advances in cardiopulmonary physiology. However, it cannot compare in content and organization to the second edition. The improvements in this edition are sufficient to constitute a new text rather than a second edition. Not only the many top quality additions, but also the changes in organization are worthy of specific comment.

Section I covers historic, anatomic and pathologic aspects of cardiovascular physiology. Section II proceeds in an orderly fashion through clinical evaluation and special technics of electrocardiography, vectorcardiography, phonocardiography, roentgenography, cinematography, and cardiac catheterization. Section III considers specific congenital and acquired diseases. The book could easily have been divided into two volumes with Section IV forming a bridge between them. This section includes a number of lucid descriptions of related functions of the heart and lungs. Sections V and VI cover general considerations and specific methods of evaluating pulmonary function. Sections VII, VIII and IX contain numerous approaches to restrictive and obstructive patterns of impairment of pulmonary function in specific diseases, followed in Section X by considerations of physiologic therapy. The short Section XI depicts some aspects of intramediastinal disease related to cardiopulmonary function. A most unique final section describes special environmental influences of our modern age including atmospheric pollution, extreme variations in altitude, and thermal and physical trauma to the thoracic structures.

The physical and scientific proportions of this volume are heavy and the book is not recommended for the casual reader except as he might wish to read a few limited chapters. The material is presented most appropriately for the physician or surgeon who has a serious major interest in the thoracic field. Many chapters should be considered as scientific essays, and because of multiple authorship, there is considerable overlap in the presentation of material. This is disadvantageous only in that it increases the size of the volume beyond what some readers might consider ideal. Nevertheless, the obvious advantages include presentation of honest differences of opinion and interpretation by various experts in the field. This book represents possibly the finest collaborative effort of a learned society pledged to the continuing education of its members and friends.

R. Drew Miller, M.D.



HOLLIS EUGENE JOHNSON, M.D.

HOLLIS EUGENE JOHNSON

TAKES OFFICE AS COLLEGE PRESIDENT

Dr. Johnson was born in Weakley County, Tennessee, on April 11, 1893. He attended elementary school in Weakley County, Jackson High School and Union University in Jackson, Tennessee, and received his degree of Doctor of Medicine from Vanderbilt University in 1921. Dr. Johnson has been associated with Vanderbilt University ever since his medical school days, having been appointed Assistant in Anatomy in 1917 and attaining the position of Professor of Clinical Medicine in 1955. In 1958, Dr. Johnson was made Professor Emeritus of Clinical Medicine. He also holds the title of Consultant in Clinical Medicine at Meharry Medical School.

In 1921-1922, Dr. Johnson interned at Davidson County Tuberculosis Hospital and in 1922-1923 served as Resident Physician at Vanderbilt University Hospital. During the period 1926-1958 Dr. Johnson served as Founder, Visiting Physician and Director of the Chest Clinic at Vanderbilt Hospital. He is also associated as Consultant at the Baptist Hospital and St. Thomas Hospital, a Staff Member at the Nashville General Hospital, Consultant in Diseases of the Chest (Dean's Committee) at Thayer Veterans Hospital, and was Founder and Director of a Clinic for Tuberculous Children, Health Department, City of Nashville (1923-1940).

A Fellow of the American College of Chest Physicians for many years, Dr. Johnson has served as a member of the Council of Postgraduate Medical Education and various committees, a member of the Board of Regents, and an Associate Editor for the College journal, *Diseases of the Chest*. He has also served as Secretary and President of the Southern Chapter of the College. Dr. Johnson belongs to a number of other medical associations, including the Nashville and Davidson County Academy of Medicine (President, 1952), Middle Tennessee Medical Association (Past President), Tennessee Medical Association, Southern Medical Association, Tennessee Thoracic Society (Past President and Founder), Nashville Thoracic Society (Past President and Founder), American Thoracic Society, National Tuberculosis Association, American Association for Thoracic Surgery, American College of Physicians, Vanderbilt Medical Association, and has served as a member of the House of Delegates of the American Medical Association. Dr. Johnson is a Diplomate of the American Board of Internal Medicine. He is also a member of many civic organizations such as the Tennessee Division of the American Cancer Society, Civil Defense Council, Nashville Chamber of Commerce, American Legion, Board of Trustees of Belmont College, and the Nashville Chapter of American Red Cross. Dr. Johnson has published numerous papers in various medical journals.

Dr. Johnson and his wife, Frances, have three married sons; Hollis Eugene Johnson, III; and twins, Robert Marshall Johnson, M.D., and John Settle Johnson, M.D. They have one grandson.

CHAPTER NEWS

Middle East Chapter

The Middle East Chapter of the College will hold its Sixth Annual Meeting in Baghdad, Iraq, November 2-5, 1961. The opening session will be devoted to "Corticotherapy in Tuberculosis." The subject for the second day will be "Chronic Pulmonary Heart," with papers on other aspects of diseases of the chest. In addition to the scientific sessions, a social program, including sightseeing and visits to medical centers, has been arranged.

West Pakistan Chapter

Members of the College met in Karachi recently to form the West Pakistan Chapter, the 82nd chapter of the College. The following officers were elected:

President	A. M. Kassim, Karachi
Secretary	Abdul Latif Minhas, Karachi

NEW CHAPTER OFFICERS

Alabama Chapter

President	Norman Van Wezel, Foley
Vice President	Leon J. Tune, Decatur
Secretary-Treasurer	Charles R. Kessler, Birmingham (re-elected)

California Chapter

President	John M. Baker, Sacramento
Vice President	Francis J. Curry, San Francisco
Secretary-Treasurer	Homer D. Peabody, Jr., San Diego

Colorado Chapter

President	Leroy Elrick, Denver
Vice President	Roger S. Mitchell, Denver
Secretary-Treasurer	D. Armin Fischer, Denver (re-elected)

Finnish Chapter

President	Pentti I. Halonen, Helsinki
Secretary	Leo Noro, Helsinki
Treasurer	Aarne N. Kuusisto, Helsinki

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President	Jiro Ishida, Tokyo
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President	Herbert C. Sweet, St. Louis
President Elect	Florence MacInnis, Kansas City
Secretary-Treasurer	David Nafe Kerr, St. Louis (re-elected)

Ohio Chapter

President	Joseph F. Tomashefski, Columbus
Vice President	Harold G. Curtis, Cleveland
Secretary-Treasurer	Francis G. Kravec, Youngstown (re-elected)

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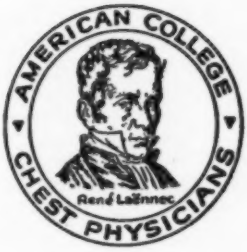
President	Alphonse L'Esperance, Ste. Foy
1st Vice President	Jonathan F. Meakins, Montreal
2nd Vice President	Andre Mackay, Montreal
Secretary-Treasurer	Philippe Emile Duval, Noranda

DISEASES *of the* CHEST



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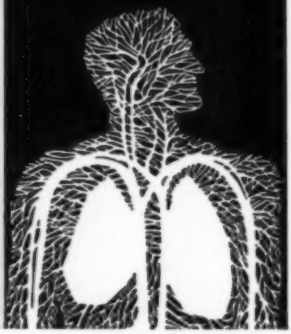
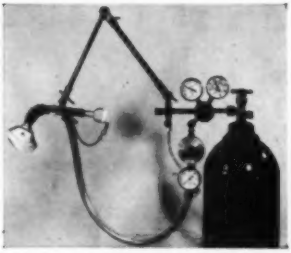
I.P.P.B. with AIR or OXYGEN: your choice with M-S-A® Pulmonary Ventilators



This is the compressor model used for air mixtures.

Other models are available for 100% oxygen or air-oxygen mixtures. Also, "total flow" Heated Mainstream Nebulizer available for all models.

Write for descriptive literature or ask for a demonstration.



Cylinder Model

MSA SAFETY EQUIPMENT HEADQUARTERS

Mine Safety Appliances Company
201 North Braddock Avenue
Pittsburgh 8, Pennsylvania

SIMPLIFIES TUBERCULIN TESTING
STERNEEDLE* GUN

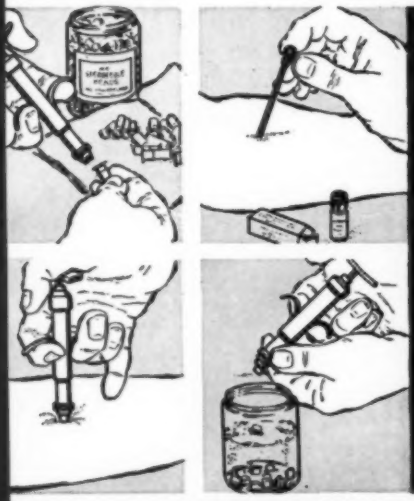
The Automatic TB Case-Finding Device for the Heaf TUBERCULIN TEST

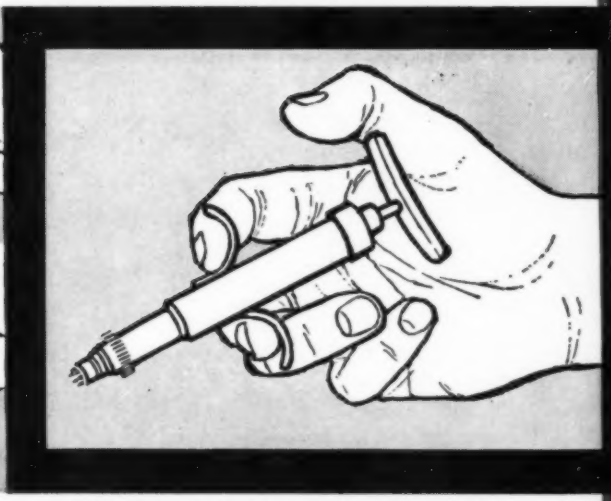
The STERNEEDLE gun is an improved multiple puncture apparatus for rapid intradermal tuberculin testing. Based on the Heaf principle of multiple puncture, six needles contained within the STERNEEDLE cartridge mechanically and painlessly penetrate the skin through a previously applied film of concentrated PPD. Needle puncture and withdrawal is automatic.

ADVANTAGES...

- **Four (4) times faster than Mantoux.**
- **Faster and more reliable than Patch test.**
- **Performs up to 400 tests per hour.**
- **Detects reactors to 5 TU Mantoux and some 100 TU reactors.**
- **No dressing required.**
- **Accurate interpretation, without measurement. Averages 250 readings per hour.**
- **Each test is uniform—puncture of 1 mm. depth and needle withdrawal is automatic.**
- **No special skill required.**
- **Painless. Ideal for testing children.**
- **Eliminates hazardous and uncertain flame sterilization.**
- **Disposable needle cartridges ELIMINATE CROSS-INFECTION.**
- **Low cost STERNEEDLE cartridges may be resterilized.**

Note: CONCENTRATED TUBERCULIN PPD 'CONNAUGHT' is used for the STERNEEDLE test. Available in 1 cc vials (sufficient for as many as 200 tests).





Procedure for STERNEEDLE TUBERCULIN TEST:

Top, left... Slip needle cartridge on gun with plastic applicator. Remove applicator.

Top, right... Place a drop of tuberculin PPD on cleansed forearm.

Bottom, left... Place gun on drop of tuberculin PPD. Pressure and release of handle automatically triggers and retracts the needles.

Bottom, right: Disposable needle cartridges and applicators may be washed and sterilized for reuse, if desired.

Write for literature. Personal demonstration may be arranged.

TARGET POINT CASE FINDING

THE Panray CORP.

266 South Dean Street, Englewood, New Jersey

*Trademark. Pat. Pend.

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